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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073, Amendment 622
Sponsor	ModernaTX, Inc
Submission Date	April 7, 2023
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Signatory Authority	David C. Kaslow, M.D., Director, OVRR
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Review Completion Date	April 17, 2023
Established Name/Names Used During Development	Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Dosage Forms/Strengths and Route of Administration	A 0.25 mL or 0.2 mL suspension for intramuscular injection (for 6 months through 5 years, depending on dose number) A 0.25 mL suspension for intramuscular injection (for 6 years through 11 years of age) A 0.5 mL suspension for intramuscular injection (for 12 years through 17 years of age) For dosing regimen, dose, and schedule, see Section 5.1
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 6 months of age and older

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1 Executive Summary

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an ongoing global health challenge. As of April 12, 2023, SARS-CoV-2 has led to over 763 million cases of coronavirus disease 2019 (COVID-19), including 6.9 million deaths worldwide. 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 to 17 years of age. The vaccine was also previously authorized for booster vaccination of individuals 18 years of age and older; however, following emergence of the Omicron variant and its sublineages (most recently BA.4/BA.5 and related 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. 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, and 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 years through 17 years of age. Finally, on December 8, 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 months through 5 years of age.

Although the available evidence suggests that the Original Moderna COVID-19 Vaccine (monovalent vaccine) continues to provide protection against serious disease from COVID-19, since the authorizations of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as boosters in children and adults, data have emerged indicating that the bivalent vaccine provides improved protection compared to the Original Moderna COVID-19 Vaccine. In addition, data from several studies provide evidence that two or more exposures to the SARS-CoV-2 Spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals. Additionally, data from the Centers for Disease Control and Prevention (CDC) indicate that most individuals over 4 years of age have either received COVID-19 vaccination, experienced infection with SARS-CoV-2, or have experienced both. In addition, simplification of the vaccine regimen is warranted. FDA expects that simplification of the immunization schedules may contribute to more facile vaccine deployment, fewer vaccine administration errors, and less complex communication, all potentially leading to improved vaccine coverage rates and, ultimately, to enhanced public health.

ModernaTx Inc., has submitted a request on April 7, 2023, to amend the EUA for consolidating the fact sheets and to update the dosing and administration schedule for Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to provide for the use of the Moderna COVID-19 Vaccine, Bivalent vaccine as a two-dose schedule for children 6 months through 5 years of age and as a single dose for individuals 6 years of age and older. In addition, ModernaTX Inc., requested to amend the EUA to provide for authorization of an additional dose of Moderna COVID-19 Vaccine, Bivalent in individuals 65 years of age and older and one or more additional doses for certain immunocompromised individuals.

Given that the Moderna COVID-19 Vaccine, Bivalent is manufactured using the same process as the Original Moderna COVID-19 Vaccine, postmarketing safety for Moderna COVID-19 Vaccine were considered relevant to the safety evaluation of Moderna COVID-19 Vaccine, Bivalent. Review of postmarketing safety data indicate a similar safety profile of the Original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of April 5, 2023, more than 249 million doses of the original Moderna COVID-19 Vaccine have been administered in the US, including 20,076,974 booster doses of the updated Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Of the total doses of either the Original or Bivalent formulation given in the US, 1,541,532 have been administered to individuals 6 months through 5 years of age and 603,947 have been administered to individuals 6 through 17 years of age, and 247,055,007 doses administered to adults ages 18 years and older (data lock point April 5, 2023).

In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain. For important risks identified in the pharmacovigilance plan for Moderna COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/postmarketing studies for the Original Moderna COVID-19 Vaccine, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting 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 adverse events of special interest (AESIs) in all ages in the general US population.

The totality of scientific evidence available currently supports moving to a single vaccine composition for all vaccine doses, consisting for the time being of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Review of the totality of the available evidence on prior exposure to SARS-CoV-2 and vaccination against COVID-19 suggests that most individuals may only need to receive one dose of a bivalent COVID-19 vaccine to restore protective immunity for a period of time. Additional doses of a bivalent COVID-19 vaccine may be reasonably expected to induce the expected protective immunity for those who have a low likelihood of prior SARS-CoV-2 infection (the very young) or those who may not generate a protective immune response (older and immunocompromised individuals). At this time the available evidence indicates that those 6 months through 5 years of age should still receive two doses of Moderna COVID-19 Vaccine, Bivalent 1 month apart; those 65 years of age and older may receive a second dose at least 4 months following administration of a prior bivalent COVID-19 vaccine; those 6 years of age and older with certain kinds of immunocompromise (solid organ transplant recipients and those determined to have a similar level of immunocompromise), may receive additional vaccine doses at least 2 months following administration of a prior COVID-19 vaccine and then subsequently at the discretion of the healthcare provider; and those 6 months through 5 years of age with certain kinds of immunocompromise who have received two doses (Moderna COVID-19 Vaccine or Moderna COVID-19 Vaccine, Bivalent) may receive additional Moderna COVID-19 Vaccine, Bivalent doses at least 1 month following the most recent dose and then subsequently at the discretion of the healthcare provider.

Taken together, the review team recommends discontinuation of use of the monovalent Moderna COVID-19 in the United States and use of the Moderna COVID-19 Vaccine, Bivalent

(Original and Omicron BA.4/BA.5) administered in an appropriate schedule based on age, vaccination status, and risk of COVID-19-associated severe disease, hospitalization, and death.

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. As of April 8, 2022, SARS-CoV-2 has led to over 762 million cases of coronavirus disease 2019 (COVID-19), including 6.8 million deaths worldwide.[1] Disease symptoms vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions,[2] may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome, leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks but symptoms may persist for months in some individuals.[3] Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults but are generally milder, with fever and cough most commonly reported.[4,5] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[4] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15% to 50% of infections.[6,7] However, COVID-19- associated hospitalizations and deaths have occurred in individuals 17 years of age and younger, and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.

In the US, more than 104 million cases and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[8] Approximately 4% of cases occurred in children less than 5 years of age and 14% of cases occurred in children and adolescents 5 through 17 years of age.[9] Since the start of the pandemic caused by the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as the ancestral, original, or reference strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron. The Omicron BA.1 variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including the recent BA.4 and BA.5 sublineages, and most recently the XBB.1.5 sublineage which accounts for nearly all reported COVID-19 cases in the US currently.[10] In addition, population- level evidence suggests an increased reinfection risk associated with the Omicron variant and its sublineages compared to earlier SARS-CoV-2 variants.[11] Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see Section 3.1 below). Since the introduction of the bivalent COVID-19 (Original + BA.4/BA.5) boosters, multiple studies have demonstrated that bivalent vaccine booster doses have provided improved protection against symptomatic disease, hospitalization, and death from the more

recently evolved Omicron sublineages that have included BA.4, BA.5, BQ.1.1, and XBB.1.5, documenting the benefit of updating the strain composition of the vaccines.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1.1, or XBB.1.5 lineage, as specified.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

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

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains nucleoside-modified mRNA that encodes for the full-length spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a: 2-dose primary series for individuals 6 months of age and older, and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 6 months through 5 years of age, to be administered at least 2 months after either completion of primary vaccination with Moderna COVID-19 Vaccine, or for those 6 years of age or older at least 2 months after completion of primary vaccination or 2 months after receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years old and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months through 5 years of age and older is 10 µg in 0.2 mL, for use in individuals 6 years through 11 years of age is 25 µg in 0.25 mL, and for use in individuals 12 years of age and older is 50 µg in 0.5 mL. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

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

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: part of 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. For children 6 months through 4 years of age, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is authorized as a single booster dose after completion of primary vaccination with three doses of Pfizer-BioNTech COVID-19 Vaccine and as the third dose of a 3-dose primary series. 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 and booster doses) 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 first homologous or heterologous booster dose (the dosing interval for a booster is at least 2 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine). 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 as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a 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. The immune modulator Olumiant (baricitinib) is currently approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The immune modulator Actemra (tocilizumab) is currently approved 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.

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

Oral antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Lagevrio (molnupiravir) is authorized for the treatment of mild-to-moderate COVID-19 in certain adults who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them. These include: sotrovimab; REGEN-COV (casirivimab and imdevimab) (both authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death); and bebtelovimab, was previously authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. For a similar reason, Evusheld (tixagevimab co-packaged with cilgavimab) is not currently authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

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

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV) or ECMO. Vilobelimab a recombinant chimeric monoclonal IgG4 antibody that specifically binds to the soluble human complement split product C5a after cleavage from C5 to block its interaction with the C5a receptor, both of which are components of the complement system thought to contribute to inflammation and worsening of COVID-19.

Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR). Anakinra is an Interleukin-1 (IL-1) receptor antagonist. IL-1 is involved in inflammatory diseases and additionally, IL-1 is linked to acute severe lung inflammation in COVID-19.

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

3 Rationale for Bivalent Strain Composition

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

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

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

Following introduction of the Bivalent (Original and Omicron BA.4/BA.5) mRNA COVID-19 vaccines, studies have demonstrated that when given to adults a single bivalent booster vaccine increases immunogenicity against currently circulating variants and reduces symptomatic disease, hospitalization, and death. [23, 24, 25, 26, 27, 28]

The improved protection against currently circulating variants provided by the bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines compared with the monovalent Original COVID-19 vaccines provides support for the transition to use of bivalent vaccines for all doses for mRNA COVID-19 vaccines as well as support for periodic updates of the strain composition of COVID-19 vaccines.

3.2 January 26, 2023, VRBPAC and Subsequent Regulatory Discussions

At the January 26, 2023, VRBPAC meeting, the committee discussed harmonization of the strain composition for primary series and booster doses, simplification of the immunization schedule, and periodic updates of COVID-19 vaccine strain composition. The committee unanimously voted in favor of harmonizing the COVID-19 vaccine strain composition for primary series and booster doses in the US to a single composition. The committee generally agreed that simplification of the immunization schedule was highly desirable and recommended that the simplification be based on the best available evidence.

In March 2023, FDA notified COVID-19 vaccine manufacturers that they should plan to implement the proposals discussed at the VRBPAC and supported by the committee's vote and discussion. Specifically, FDA noted that the process of moving to a single vaccine strain composition, i.e., Original and Omicron BA.4/BA.5 for all mRNA-based COVID-19 vaccines, should also involve consolidation of the various provider and patient fact sheets for different age groups into one provider and one patient fact sheet for each vaccine, and simplification of the vaccination regimens to the extent appropriate. Specifically, given the current state of immunity of the population, including naturally acquired, vaccine-induced, and hybrid (combined natural infection in the setting of at least one COVID-19 vaccination) immunity, FDA suggested moving to a single vaccination for most individuals for each of the authorized bivalent vaccines, with modifications for the very young, those 65 years and older, and those with certain forms of immunocompromise. The current EUA request was made in response to this recommendation by FDA.

4 Regulatory Considerations for EUA of a Bivalent COVID-19 Vaccine with an Omicron Component

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

The Secretary of the US Department of Health and Human Services (HHS) has determined that there is a public health emergency or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. Based on that determination, and the Secretary's declaration that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, FDA may issue an EUA after determining that certain statutory requirements are met [section 564 of the FD&C Act (21 U.S.C. 360bbb-3)].

- The chemical, biological, radiological, or nuclear (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 expectations.

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 nor simplification of authorized dosing regimens and schedules, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. 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.

The guidance recommended that studies to demonstrate effectiveness of a monovalent modified COVID-19 vaccine administered for primary vaccination use a dose and dosing regimen that is the same as the authorized prototype vaccine, and a study is underway for the use of a two-dose regimen of the Moderna COVID-19 Vaccine, Bivalent. At this time, FDA considers it reasonable to authorize a two-dose regimen of the Moderna COVID-19 Vaccine, Bivalent in previously unvaccinated individuals 6 months to 5 years of age given the anticipated favorable benefit-risk balance of this regimen in that age group. FDA also considers it reasonable to authorize additional doses of the Moderna COVID-19 Vaccine, Bivalent in individuals 65 years of age and older and certain immunocompromised individuals given the anticipated favorable benefit-risk balance of additional doses in those individuals. This is based upon the accumulated experience with primary series, first booster doses, and second booster doses of the Moderna COVID-19 Vaccine, and booster doses of the Moderna COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.1) (see Section 6).

5 EUA Amendment Request to Consolidate the Fact Sheets and Update Dosing and Administration for the Moderna COVID-19 Vaccine, Bivalent

5.1 Summary of the EUA Request

On April 7, 2023, Moderna submitted a request to amend the EUA to update the dosing and administration schedule for Moderna COVID-19 Vaccine Bivalent (Original and Omicron BA.4/BA.5), including the use of the bivalent vaccine as a 2-dose schedule for children 6 months through 5 years of age and a single dose vaccination schedule for most individuals 6 years of age and older, consistent with the following tables:

Table 1. Individuals 6 Months of Age and Older Not Previously Vaccinated with Any COVID-19 Vaccine

Age	Moderna COVID-19 Vaccine, Bivalent Vial Cap and Label Color	Dosing Regimen, Dose, and Schedule
6m-5y	Dark Blue Cap and a Label with Gray Border	2 doses, 0.25 mL each Dose 1: month 0 Dose 2: month 1
6-11y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.25 mL
12-64y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.5 mL

Age	Moderna COVID-19 Vaccine, Bivalent Vial Cap and Label Color	Dosing Regimen, Dose, and Schedule
≥65y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.5 mL One additional dose, 0.5 mL, may be administered ≥4 months after first dose of an authorized bivalent COVID-19 vaccine

Table 2. Individuals 6 Months Through 5 Years of Age Previously Vaccinated with Moderna COVID-19 Vaccine

Age	Number of Previous Doses of Moderna COVID-19 Vaccine	Moderna COVID-19 Vaccine, Bivalent Vial Cap and Label Color	Dosing Regimen, Dose and Schedule
6m–5y	1 previous dose	Dark Blue Cap and a Label with Gray Border	Single Dose, 0.25 mL One month after receipt of Moderna COVID-19 Vaccine
6m–5y	2 previous doses	Dark Pink Cap and a Label with a Yellow Box	Single dose, 0.2 mL ≥2 months after receipt of Moderna COVID-19 Vaccine

Table 3. Individuals 6 Years of Age and Older Previously Vaccinated with 1 or More Doses of Any Monovalent COVID-19 Vaccine

Age	Moderna COVID-19 Vaccine, Bivalent Vial Cap and Label Color	Dosing Regimen, Dose and Schedule
6-11y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.25 mL ≥2 months after monovalent COVID-19 vaccine
12-64y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.5 mL ≥2 months after monovalent COVID-19 vaccine
≥65y	Dark Blue Cap and a Label with Gray Border	Single dose, 0.5 mL ≥2 months after monovalent COVID-19 vaccine One additional dose, 0.5 mL, may be administered ≥4 months after first dose of an authorized bivalent COVID-19 vaccine

In addition, for certain immunocompromised individuals 6 months through 5 years of age, who have received two doses of Moderna COVID-19 Vaccine or Moderna COVID-19 Vaccine, Bivalent, the EUA request encompassed an additional 0.25 mL dose of Moderna COVID-19 Vaccine, Bivalent administered at least 1 month following the most recent dose. The EUA request also encompassed additional doses of Moderna COVID-19 Vaccine, Bivalent at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.

The EUA request also encompassed a single additional age-appropriate dose of Moderna COVID-19 Vaccine, Bivalent for certain immunocompromised individuals 6 years of age and older, at least 2 months following the initial dose of a bivalent COVID-19 vaccine and subsequent age-appropriate doses of Moderna COVID-19 Vaccine, Bivalent for these individuals at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.

5.2 FDA Approach to Harmonizing the Strain Composition and Simplifying the Immunization Schedule

5.2.1 Harmonizing the Strain Composition

Multiple variants of SARS-CoV-2 have emerged since the beginning of the pandemic. After the emergence and rapid global spread of the Omicron variant (B.1.1.529, also referred to as the BA.1 sublineage) and more recent predominance of the Omicron BA.4 and BA.5 sublineages (hereafter referred to as BA.4/BA.5 due to the shared structure of their spike glycoproteins), along with clinical trial and real-world data indicating waning protection following primary series and booster doses of available COVID-19 vaccines, and reduced effectiveness of currently available original (monovalent) COVID-19 vaccines against Omicron BA.4/BA.5, 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.

Recent pre-clinical data supports the improved antibody response of bivalent vaccines (compared to monovalent vaccine) against Omicron variants when used in naïve animals,[29] as does recent clinical and real world effectiveness from studies with bivalent vaccines.

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

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

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

Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Moderna COVID-19 Vaccine, FDA determined that it was reasonable to extrapolate the available safety, efficacy, immunogenicity, and real-world evidence supporting a favorable benefit-risk balance for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk balance for use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a single dose in individuals 6 years of age and older administered at least 2 months after receipt of a monovalent COVID-19 vaccine.

As mentioned in Section 4.2 above, FDA considers that safety and effectiveness data for a bivalent COVID-19 vaccine accrued in a certain age group could be extrapolated to support emergency use authorization in other age groups. Accumulated experience with mRNA COVID-

19 vaccines has demonstrated that while some differences in safety profile and magnitude of neutralizing antibody responses are apparent across various age groups, there is an overall similarity in safety profile and immune response across age groups. FDA therefore considers that it is reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine to any age group for which available evidence has supported (or would support) emergency use authorization of a prior COVID-19 vaccine manufactured by the same process as the bivalent vaccine.

5.2.2 Simplification of Immunization Schedule

One approach to immunization schedule simplification relies upon evidence that two or more exposures to the SARS-CoV-2 Spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals.

Evidence supportive of this approach includes the following:

- Seroprevalence surveys estimate that almost all the US population 5 years of age and older now have antibodies (from vaccination and/or infection) against SARS-CoV-2 (Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, March 31. https://covid.cdc.gov/covid-data-tracker).
- Multiple studies that report that at least two exposures to S protein, through vaccination and/or infection, provide some degree of protective immunity. High-level summaries of some of these published studies are provided as follows:

    - Powell et al. 2022[28] reported that previous infection with any SARS-CoV-2 variant alone provided some protection in adolescents against symptomatic reinfection with another variant, while vaccination added to this protection. Vaccination alone provided low-to-moderate protection against symptomatic Omicron infection in adolescents with waning protection after each dose. Authors note that hybrid immunity (from previous infection irrespective of variant plus vaccination) offered the highest protection against Omicron infection.
    - Hansen at al. 2022[27] reported that previous Omicron infection in triple vaccinated individuals in Denmark provided high-level protection against BA.5, supporting the notion that vaccination can boost preexisting hybrid immunity and lead to protection against infection by variants.
    - Flury et al. 2022[24] reported that hybrid immunity and booster vaccination in health professionals were associated with reduced risk of fewer reported symptoms during SARS-CoV-2 infection during the Delta and Omicron waves in Switzerland. Booster vaccination in uninfected individuals was associated with reduction in risk of symptomatic Omicron infection while this immunity was found to wane over time.
    - Chin et al. 2022[26] reported data from effectiveness studies in two high-risk populations in a prison system. Preexisting immunity generated through infection alone or a combination of mRNA vaccination (two or three doses) and previous infection (hybrid immunity) was effective in preventing Omicron infection.

Immunization with three doses of mRNA vaccine was associated with the highest protection compared to two doses, even in previously infected individuals.

- Andeweg et al. 2022[23] reported that a combination of previous infection and primary vaccination provided better protection against Omicron infection than either one alone. Boosting offered highest protection even in previously infected individuals. Protection was found to be similar in individuals who were infected first followed by vaccination or who were vaccinated first followed by infection, indicating that order of infection or vaccination did not influence protection offered by hybrid immunity.
- Bates et al. 2022[25] found that individuals who had breakthrough infections after vaccination and those who were vaccinated after a natural infection neutralized SARS-CoV-2 infections to a similar degree. Hybrid immunity was observed irrespective of the order of infection and vaccination and broadly neutralized SARS-CoV-2 variants to a similar degree.

Although all the above studies generally support a simplified immunization schedule based upon two or more exposures to S protein through vaccination and/or infection, interpreting the data from these studies is complicated because of the diversity of study designs, populations studied, and clinical endpoints used. Of note, some other studies highlight evidentiary inconsistencies regarding the need for a periodic (e.g., annual) dose of an approved or authorized COVID-19 vaccine to restore protective immunity in immunocompetent individuals. High-level summaries of two such published studies are provided as follows:

- Carazo et al. 2023 [30] reported that health-care workers who acquired hybrid immunity through the receipt of two doses of mRNA vaccine and a previous BA.1 infection were subsequently well protected for a prolonged period against BA.2 reinfection and a third vaccine dose did not offer improvement to the protection conferred by “pre-existing hybrid immunity.” The authors of this study noted that if the protection from pre-existing hybrid immunity also pertains to future variants, there might be limited benefit from additional vaccine doses for people with hybrid immunity, depending on timing and variant.

- Carazo et al. 2022 reported that a third vaccine dose in twice-vaccinated individuals who had had a non-Omicron SARS-CoV-2 infection offered limited protection against Omicron-associated hospitalization. [31]

At this time, the totality of the evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies, support administration of a single dose of Moderna COVID-19 Vaccine, Bivalent for most of the US population 6 years of age and older.

5.3 Basis for EUA Revision to Remove Authorization for Use of the Moderna COVID-19 Vaccine in the US and Clarify Export Conditions

FDA may revise or revoke an EUA if the circumstances justifying its issuance (under section 564(b)(1) of the FD&C Act) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety (see section 564(g)(2) of the FD&C Act).

Currently, circumstances exist that make it appropriate to revise the Moderna COVID-19 Vaccine EUA to protect the public health. As outlined in Section 2.2, the monovalent Moderna COVID-19 Vaccine is authorized for use as 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 kinds of immunocompromise. FDA's revisions to the EUA for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to authorize its use in individuals 6 months of age and older, as described in the EUA request, is being considered for the express purpose of improving protection against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as compared to the monovalent Moderna COVID-19 Vaccine. In addition, the revision is being considered to help simplify COVID-19 vaccine composition and dosing schedules in the United States, which should reduce complexity, decrease vaccine administration errors due to the complexity of the number of different vial presentations, and potentially increase vaccine uptake. Consequently, at this time, revising the Moderna COVID-19 Vaccine EUA to remove its authorization for use in the United States is appropriate to protect the public health.

That said, the considerations about simplifying the U.S. vaccination schedule are not applicable when the vaccine is used in other countries, and existing supplies of the monovalent Moderna COVID-19 Vaccine may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks, when used in accordance with the current authorization. In addition, all other requirements in section 564(c) of the FD&C Act continue to be met with respect to the uses for which the Moderna COVID-19 Vaccine is currently authorized. Therefore, it is appropriate to continue to authorize the Moderna COVID-19 Vaccine for export.

Accordingly, authorization of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months of age and older as described in the EUA request, would be accompanied by the revision of the authorization for the monovalent Moderna COVID-19 Vaccine to remove its authorization for use in the United States but permit its continued export under the EUA, subject to specific conditions. These conditions include, among other things, that the regulatory authorities of the countries in which the vaccine will be used are informed that the Moderna COVID-19 Vaccine and associated Fact Sheets are no longer authorized for use in the United States and that FDA is no longer revising those Fact Sheets with updated information. These conditions also include a requirement to provide the regulatory authorities, upon request, with the currently authorized Fact Sheets. These conditions will ensure that the regulatory authorities in destination countries have relevant information with respect to the vaccine.

6 FDA Review of Clinical Effectiveness and Safety Data

6.1 Overview of Clinical Studies

Please refer to prior FDA memoranda for detailed review of the data supporting authorization of the Original Moderna COVID-19 Vaccine and the Moderna Vaccine, Bivalent (Original and Omicron BA.4/BA.5). A high-level summary of prior data reviewed and additional evidence relevant to the change to use of one vaccine composition [i.e., Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] and material supporting the updated vaccination schedule described in the EUA request are provided here.

6.2 Effectiveness of a Single Dose of Moderna COVID-19 Vaccine, Bivalent for 6 years of age and older

6.2.1 Establishing Efficacy of Moderna COVID-19 Vaccine

6.2.1.1 Efficacy of 2-Dose Primary Series of Moderna COVID-19 Vaccine in Participants 18 Years of Age and Older

Study 1 was a Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of Moderna COVID-19 Vaccine in participants 18 years of age and older in the United States (NCT04470427). Randomization was stratified by age and health risk: 18 to <65 years of age without comorbidities (not at risk for progression to severe COVID-19), 18 to <65 years of age with comorbidities (at risk for progression to severe COVID-19), and 65 years of age and older with or without comorbidities. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable human immunodeficiency virus (HIV) infection. A total of 30,420 participants were randomized equally to receive 2 doses of the Moderna COVID-19 Vaccine (100 µg mRNA per dose) or saline placebo 1 month apart. Participants were followed for efficacy and safety until 24 months after the second dose.

The primary efficacy analysis **population** (referred to as the Per-Protocol Set) included 28,207 participants who had a negative baseline SARS-CoV-2 status and received two doses (0.5 mL at 0 and 1 month) of either Moderna COVID-19 Vaccine (100 µg mRNA; n=14,134) or placebo (n=14,073). The median length of follow-up for efficacy for participants in the study was 9 weeks post-Dose 2.

In the final scheduled primary efficacy analysis of PCR-confirmed and adjudicated COVID-19 cases, vaccine efficacy after 14 days post dose 2 was 94.1% (95% CI: 89.3%; 96.8%). Efficacy outcomes were high across demographic subgroups [e.g., in 18 to <65 years of age, 95.6% (95% CI: 90.6%; 97.9%); in 65 years of age and older, 86.4% (95% CI: 61.4%; 95.2%)] and in participants with medical comorbidities associated with higher risk of severe COVID-19. A secondary efficacy analysis using a more severe COVID-19 case definition included 30 adjudicated cases in the placebo group and none in the vaccine group (though one severe case in the vaccine group was confirmed after this analysis). Additional post-hoc efficacy analyses also suggested efficacy against COVID-19 in the time period between dose 1 and dose 2.

Based on adequate and well-controlled trials in participants 18 years of age and older, the vaccine efficacy data of the Moderna COVID-19 Vaccine provided compelling direct evidence of clinical benefit and an efficacy foundation for immunobridging.

Please refer to section 4.2 of the EUA memorandum dated December 18, 2020 for a detailed review.

6.2.1.2 Efficacy of 2-Dose Primary Series of Moderna COVID-19 Vaccine in Participants 12 Through 17 Years of Age

Study 3 is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the safety, reactogenicity, and effectiveness of Moderna COVID-19 Vaccine in adolescents ages 12 years through 17 years in the United States (NCT04649151). A total of

3,732 participants were randomized 2:1 to receive 2 doses of Moderna COVID-19 Vaccine (100 µg mRNA per dose) or saline placebo 1 month apart.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of May 8, 2021, was performed in 3,181 participants who received two doses (at 0 and 1 month) of either Moderna COVID-19 Vaccine (n=2,139) or placebo (n=1,042) and had a negative baseline SARS-CoV-2 status (referred to as the Per-Protocol Set for Efficacy). The median length of follow up for efficacy for participants in the study was 53 days post-Dose 2.

The vaccine efficacy against the study-defined COVID-19 starting 14 days after Dose 2 was 100% (95% CI: 28.9%; non-evaluable), with 4 cases in the placebo arm and no cases in the vaccine arm. Using the CDC case definition, vaccine efficacy was 93.3% (95% CI: 47.9%; 99.9%) with 7 cases in the placebo arm and 1 case in the vaccine arm. These results appear to be consistent with the vaccine efficacy from the adult efficacy study (P301); however, the small number of COVID-19 cases, especially using the study definition of COVID-19, resulted in large CIs.

Although based on a small number of cases, the supplementary VE data of the Moderna COVID-19 Vaccine provided supportive direct evidence of clinical benefit in addition to the vaccine effectiveness inferred by immunobridging data in the study.

Please refer to section 4.3 of the EUA Memorandum dated June 16, 2022, for a detailed review.

The totality of the vaccine efficacy data from clinical trials in participants 12 through 17 years of age, and 18 years of age and older provides compelling direct evidence of clinical benefit and establishes an efficacy foundation for immunobridging.

6.2.2 Inferring effectiveness through immunogenicity of Moderna COVID-19 Vaccine

6.2.2.1 Effectiveness of 2-Dose Primary Series of Moderna COVID-19 Vaccine in Participants 12 Years Through 17 Years of Age

Effectiveness in individuals 12 years through 17 years of age is inferred based on a comparison of immune responses in this age group to adults 18 years through 25 years of age.

In Study 3, an analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates (SSRs) 28 days after Dose 2 in a subset of adolescents 12 years through 17 years of age in Study 3 and participants 18 years through 25 years of age in Study 1 who had no immunologic or virologic evidence of prior SARS-CoV-2 at baseline.

The geometric mean 50% neutralizing titers (GMT) ratio was 1.1 (95% CI: 0.9; 1.2), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >0.8. The difference in SRRs was 0.2% (95% CI: -1.8%; 2.4%) which met the pre-specified success criterion of a LL of the 95% CI being greater than -10% and a SRR difference point estimate of -5%.

Noninferior immune responses demonstrated in a comparison of participants 12 years through 17 years of age to participants 18 years through 25 years of age supported the inference of Moderna COVID-19 Vaccine effectiveness in individuals 12 years through 17 years of age.

Please refer to section 4.3 of the EUA Memorandum dated June 16, 2022 for a detailed review.

6.2.2.2 Effectiveness of Two-Dose Primary Series of Moderna COVID-19 Vaccine in Participants 6 Years Through 11 Years of Age

Effectiveness in individuals 6 years through 11 years of age is inferred based on a comparison of immune responses in this age group to adults 18 years through 25 years of age.

Study 4 includes an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind clinical trial component to evaluate the safety, reactogenicity, and effectiveness of Moderna COVID-19 Vaccine in individuals ages 6 years through 11 years in the United States and Canada (NCT04796896). A total of 4,016 participants were randomized 3:1 to receive 2 doses of Moderna COVID-19 Vaccine (50 µg mRNA per dose) or saline placebo 1 month apart.

An analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates (SSRs) 28 days after Dose 2 in a subset of individuals 6 years through 11 years of age in Study 4 and participants 18 years through 25 years of age in Study 1 who had no immunologic or virologic evidence of prior SARS-CoV-2 at baseline.

The geometric mean 50% neutralizing titers (GMT) ratio was 1.1 (95% CI: 0.9; 1.2), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >0.8. The difference in SRRs was 0.2% (95% CI: -1.8%; 2.4%), which met the pre-specified success criterion of a LL of the 95% CI being greater than -10% and a SRR difference point estimate of -5%.

Noninferior immune responses demonstrated in a comparison of participants 6 years through 11 years of age to participants 18 years through 25 years of age supported the inference of Moderna COVID-19 Vaccine effectiveness in individuals 6 years through 11 years of age.

Please refer to section 4.3 of the EUA Memorandum dated June 16, 2022, for a detailed review of this study.

6.2.2.3 Immunogenicity of Moderna COVID-19 Vaccine Administered as a First Booster Dose Following a Primary Series of Moderna COVID-19 Vaccine in Participants 18 Years of Age and Older

Effectiveness of a booster dose of Moderna COVID-19 Vaccine was inferred based on assessment of neutralizing antibody titers (ID50) against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation. Immunogenicity analyses compared the ID50 following the booster dose to the ID50 following the primary series.

In an open-label phase of Study 2, participants 18 years of age and older received a single booster dose (50 µg mRNA; 0.25 mL) at least 6 months after completion of the primary series. The primary immunogenicity analysis population included 149 booster dose participants in Study 2 (including one individual who had only received a single dose of the primary series) and a random subset of 1,055 participants from Study 1 who had completed primary vaccination with Moderna COVID-19 Vaccine. Study 1 and 2 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively. The median age of Study 2 participants was 56 years of age (range 18-82) and 24.8% of participants were 65 years of age and older.

Immunogenicity analyses included an assessment of ID50 geometric mean titer (GMT) ratio and difference in seroresponse rates (SSRs). The geometric mean 50% neutralizing titers (GMT)

ratio was 1.8 (95% CI: 1.5; 2.1), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI >0.67 and a point estimate of >1.0. Seroresponse for a participant was defined as achieving a ≥4-fold rise in ID50 from baseline (before the booster dose in Study 2 and before the first dose of the primary series in Study 1). The lower limit of the 2-sided 95% CI for the difference in SSRs between Study 1 and Study 2 was -16.7%, which did not meet the immunobridging criterion for a booster response (lower limit of 2-sided 95% CI for the percentage difference of ≥-10%). An additional descriptive analysis evaluated SSRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. The booster dose SSR, with seroresponse defined as at least a 4-fold rise relative to the pre-Dose 1 titer, was 100%. The difference in SSRs in this post-hoc analysis was 1.6% (95% CI: -0.9%, 2.6%).

Noninferior immune responses demonstrated in a comparison of participants 18 years and older who received a booster dose to participants 18 years and older who received a primary series supported the inference of Moderna COVID-19 Vaccine effectiveness of a single booster dose (50 µg mRNA) in individuals 18 years and older.

Please refer to section 4.2 of the EUA memorandum dated December 18, 2020 for a detailed review of this study.

The totality of evidence of the immunogenicity of Moderna COVID-19 Vaccine administered as a first booster dose following a primary series of Moderna COVID-19 Vaccine in participants 18 years of age and older support the inference of Moderna COVID-19 Vaccine effectiveness of a single booster dose (50 µg mRNA) at least 6 months after completion of the primary series in individuals 18 years of age and older.

6.2.2.4 Immunogenicity of Moderna COVID-19 Vaccine Booster Dose Following Moderna COVID-19 Vaccine Primary Series in Participants 12 Years Through 17 Years of Age

Effectiveness of a booster dose of Moderna COVID-19 Vaccine in participants 12 years through 17 years of age was inferred based on a comparison of immune responses, as assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the booster dose in 12 years through 17 years of age to that following the primary series in adults 18 years through 25 years of age.

In an open-label phase of Study 3, participants 12 years through 17 years of age received a single booster dose of Moderna COVID-19 Vaccine (50 µg mRNA) at least 5 months after completion of the primary series (two doses 1 month apart). The primary immunogenicity analysis population included 257 booster dose participants in Study 3 and a random subset of 295 participants 18 years through 25 years of age from Study 1 who received two doses of Moderna COVID-19 Vaccine 1 month apart. Study 1 and Study 3 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively.

The co-primary immunogenicity analyses consisted of the geometric mean concentration (GMC) ratio and the difference in seroresponse rates (SSRs) following the booster dose in Study 3 (adolescents) compared to SSRs after the primary series in Study 1 (young adults). Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in Study 1 and Study 3).

The GMC ratio was 5.1 (95% CI: 4.5; 5.8), which met the pre-specified success criteria of a lower bound (LB) of the 95% CI ≥ 0.67 and a point estimate of ≥ 0.8. The difference in SRRs

was 0.7% (95% CI: -0.8; 2.4), which met the pre-specified success criterion of a LB of the 95% CI ≥ -10%. FDA requested a post hoc analysis using a revised seroresponse definition based on the proportion of adolescent participants achieving a ≥ 4-fold rise in GMCs from the pre-booster time point. The booster dose SSR was 96.5%. The difference in SSRs in adolescents compared young adults was -2.8% (95% CI -5.9%; -0.6%).

Noninferior immune responses demonstrated in a comparison of participants 12 years through 17 years of age to participants 18 years through 25 years of age support the inference of Moderna COVID-19 Vaccine effectiveness of a single booster dose (50 µg mRNA) in adolescents 12 years through 17 years of age.

Please refer to section 6.3 of the EUA memorandum dated October 11, 2022 for detailed review.

6.2.2.5 Immunogenicity of Moderna COVID-19 Vaccine Booster Dose Following Moderna COVID-19 Vaccine Primary Series in Participants 6 Years Through 11 Years of Age

Effectiveness of a booster dose of Moderna COVID-19 Vaccine in participants 6 years through 11 years of age was inferred based on a comparison of immune responses, as assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the booster dose in participants 6 years through 11 years of age to that following the primary series in participants 18 years through 25 years of age.

In an open-label phase of Study 4, participants 6 years through 11 years of age received a single booster dose of Moderna COVID-19 Vaccine (25 µg mRNA) at least 6 months after completion of the primary series (two doses 1 month apart). The primary immunogenicity analysis population included 95 booster dose participants in Study 4 and a random subset of 295 participants 18 years through 25 years of age from Study 1 who received two doses of Moderna COVID-19 Vaccine 1 month apart. Study 1 and Study 4 participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the first primary series dose and prior to the booster dose, respectively.

The co-primary immunogenicity analyses consisted of the geometric mean concentration (GMC) ratio and the difference in seroresponse rates (SSRs) following the booster dose in Study 4 (children) compared to seroresponse rates after the primary series in Study 1 (young adults). Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in Study 1 and Study 3).

The GMC ratio was 4.2 (95% CI: 3.5; 5.0), which met the pre-specified success criterion of a lower bound (LB) of 95% CI ≥ 0.667. The difference in SRR was 0.7% (95% CI: -3.5%; 2.4%), which met the pre-specified success criterion of a LB of the 95% CI ≥ −10%.

Noninferior immune responses demonstrated in a comparison of participants 6 years through 11 years of age to participants 18 years through 25 years of age supported the inference of effectiveness of Moderna COVID-19 Vaccine as a single booster dose (25 µg mRNA) in children 6 years through 11 years of age.

Please refer to section 6.1 of the EUA memorandum dated October 11, 2022 for detailed review.

6.2.2.6 Immunogenicity of Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose in Participants 18 Years of Age and Older

Effectiveness following a booster dose of Bivalent Vaccine (Original and Omicron BA.1) in individuals 18 years and older was inferred based on a comparison of immune responses following a booster dose of Moderna COVID-19 Vaccine in participants 18 years of age and older, as assessed neutralizing antibody responses against a pseudotype virus containing the SARS-CoV-2 S protein from the Omicron BA.1 sublineage and a pseudotype virus containing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation.

Study 5 is a Phase 2/3 open-label study in which participants 18 years of age and older, who had previously received a two-dose primary series and one booster dose of Moderna COVID-19 Vaccine, received a second booster dose with the bivalent vaccine (Original and Omicron BA.1) at least 3 months after the first booster dose. The bivalent vaccine (Original and Omicron BA.1) contained a total of 50 µg mRNA per dose. The primary immunogenicity analysis population included 334 participants who received a booster dose of bivalent vaccine (Original and Omicron BA.1) and 260 participants who received a booster dose of Moderna COVID-19 Vaccine. For the bivalent vaccine (Original and Omicron BA.1) group, 195 (58.4%) participants were 18 years through 64 years of age and 139 (41.6%) were 65 years of age and older; 43.4% were male, 56.6% were female. Participants included in the analysis population had no serologic or virologic evidence of SARS-CoV-2 infection prior to the second booster dose.

The co-primary immunogenicity analyses compared the 50% inhibitory dose (ID50) GMTs and seroresponse rates (SSRs) (the proportion achieving a ≥4-fold rise in ID50 from pre-dose 1 of the primary series) 28 days following a second booster dose with bivalent vaccine (Original and Omicron BA.1) to those following a second booster dose with Moderna COVID-19 Vaccine.

The GMT ratio was 1.7 (97.5% CI 1.5; 2.0) against Omicron BA.1 and 1.2 (97.5% CI 1.1; 1.4) against the ancestral strain, both of which met the pre-specified success criteria of a lower bound (LB) of the 97.5% confidence interval (CI) ≥ 0.67. In participants 65 years of age and older, the GMT ratio was 1.5 (95% CI 1.3; 2.0) against Omicron BA.1 and 1.1 (95% CI 1.0; 1.3) against the ancestral strain.

The difference in SRRs was 1.5% (97.5% CI: -1.1%, 4.0%), which met the pre-specified success criterion of a LB of the 97.5% CI ≥ −10%. FDA requested a post hoc analysis using a revised seroresponse definition based on the proportion of participants achieving a ≥ 4-fold rise in GMTs from the pre-booster time point. The SSR following a second booster dose with bivalent vaccine (Original and Omicron BA.1) was 74.9% (95% CI: 69.8%; 79.4%) against Omicron BA.1 and 53.9% (95% CI: 48.4%; 59.3%) against the ancestral strain. The difference in SRRs was 21.6% (97.5% CI: 12.9%, 30.3%) against Omicron BA.1 and 11.2% (97.5% CI: 2.1%, 20.3%) against the ancestral strain. If the post hoc SRR analyses using the revised definition had been pre-specified with formal hypothesis testing as described in the FDA guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 (updated March 2022), then the bivalent vaccine (Original and Omicron BA.1) would have demonstrated super-superiority (a 95% CI margin >10%) against Omicron BA.1 and simple superiority (a 95% CI margin >0%) against the ancestral strain as compared to Moderna COVID-19 Vaccine. In participants 65 years of age and older, the difference in SRRs was 17.6% (97.5% CI: 4.2%, 30.5%) against Omicron BA.1 and 8% (97.5% CI: -6.0%, 21.7%) against the ancestral strain.

Immune responses, demonstrated in participants 18 years of age and older in a comparison of the Bivalent Vaccine (Original and Omicron BA.1) to Moderna COVID-19 Vaccine, supported

the inference of effectiveness of a single bivalent vaccine dose (50 µg mRNA) in individuals 18 years of age and older.

Please refer to section 6.1 in the EUA memorandum dated August 31, 2022 for detailed review.

Based on the totality of the immunogenicity data from clinical trials of the Moderna COVID-19 Vaccine and Bivalent Vaccine (Original and Omicron BA.1), it is reasonable to infer the effectiveness of Moderna Vaccine, Bivalent in individuals 18 years of age and older and to extrapolate the effectiveness of Moderna Vaccine, Bivalent in individuals 6 years through 17 years of age.

6.2.3 Inferring the Effectiveness of a Single Dose of Moderna COVID 19 Vaccine, Bivalent in Individuals with Evidence of Prior SARS-CoV-2 Infection

Recent evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection against COVID-19 and that immunity acquired by infection should be considered in determining the immunization schedule (Pilz et al 2022). With "sufficient preexisting immunity," through prior infection, vaccination, or combination thereof, administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a desired duration. Given recent seroprevalence surveys [32] and the clinical data generated with the Moderna COVID-19 Vaccine that is available for different age groups, it is appropriate to simplify the immunization schedule for the Moderna COVID-19 Vaccine, Bivalent to a single dose for most individuals 6 years of age and older.

The evidence to support inference of the effectiveness of a single dose of Moderna COVID-19 Vaccine, Bivalent in individuals with prior SARS-CoV-2 infection comes both from immunogenicity studies summarized below and from real-world data or observational studies (see Section 5.2.2).

6.2.3.1 Immunogenicity of a Single Dose of Moderna COVID 19 Vaccine Administered to Participants 6 years through 11 years of age and 18 years of age and older with Evidence of Prior SARS-CoV-2 Infection

To infer the effectiveness of a single dose of Moderna COVID 19 Vaccine in individuals with prior SARS-CoV-2 infection, FDA reviewed a post hoc analysis from clinical studies evaluating a primary series of Moderna COVID-19 Vaccine to compare baseline (pre-Dose 1) geometric mean titers (GMTs) of neutralizing antibodies against a pseudovirus expressing the original SARS-CoV-2 Spike protein (D614G) to GMTs at 28 days after Dose 1 for participants with evidence of prior SARS-CoV-2 infection and at 28 days after Dose 2 for participants without evidence of prior SARS-CoV-2 infection.

In both age groups [i.e., 6 years through 11 years of age (6-11y) and 18 years of age and older (≥18y) groups], GMTs at 28 days post-Dose 1 in participants with evidence of prior infection [in 6-11y, 2110.0 (95% CI: 845.1; 5268.4); and in ≥18y, 1478.9 (95% CI: 1069.6; 2044.9)] were not statistically different from GMTs at 28 days post-Dose 2 in participants without evidence of prior infection [in 6-11y, 1616.5 (95% CI: 1463.1; 1786.1); and in ≥18y 1081.1 (95% CI: 1019.8; 1146.1)].

Immune responses, assessed in participants 6-11y and ≥18y, comparing a single dose of Moderna COVID 19 Vaccine in participants with evidence of prior infection to two doses of Moderna COVID 19 Vaccine in participants without evidence of prior infection support the

inference of effectiveness of a single vaccine dose of 25 µg mRNA in individuals 6 years through 11 years of age who have had a prior infection and a single vaccine dose of 50 µg mRNA in individuals 18 years of age and older who have had a prior infection. Effectiveness of a single vaccine dose of 50 µg mRNA in individuals 12 years through 17 years of age who have had a prior infection is extrapolated from immune responses in participants 6-11y and ≥18y.

6.2.3.2 Effectiveness of a Single Dose of Moderna COVID 19 Vaccine, Bivalent in Individuals with Evidence of Prior SARS-CoV-2 Infection

As described in Section 5.2.2, recent evidence indicates that two or more exposures to the SARS-CoV-2 Spike protein through vaccination and/or infection provide sufficient pre-existing immunity such that administration of a single dose of an authorized bivalent COVID-19 vaccine would likely induce or restore the expected protective immunity for a defined duration in immunocompetent individuals.

Given the evidence in Section 6.2.2.6 that support the inference of the effectiveness of Moderna Vaccine, Bivalent in individuals 18 years of age and older and in Section 6.2.3.1 that support the inference of the effectiveness of a single vaccine dose of 50 µg mRNA in individuals 18 years of age and older who have had a prior infection and the extrapolation of the effectiveness of a single vaccine dose of 50 µg mRNA in individuals 12 years through 17 years of age who have had a prior infection, it is reasonable to expect a single 50 µg dose of Moderna COVID-19 Vaccine, Bivalent may induce or restore protective immunity against severe COVID-19 caused by currently circulating sublineages of Omicron in individuals 12 years of age and older.

Little real-world evidence for the effectiveness of a bivalent booster dose in 6 years through 11 years of age has been reported, largely because the bivalent booster was authorized later than for older age groups and the vaccine uptake has been lower. Given the evidence in Section 6.2.3.1 that support the inference of the effectiveness of a single vaccine dose of 25 µg mRNA in individuals 6 years through 11 years of age who have had a prior infection and given the real-world and immunogenicity studies described above and the well understood safety profile of the vaccines in this age group, it is reasonable to expect that a single dose of Moderna COVID 19 Vaccine, Bivalent in this age group will improve protection against severe COVID-19.

Based on the totality of evidence, including from seroprevalence surveys, real-world studies (see also Section 5.2.2) and immunogenicity studies, it is reasonable to expect that in most of the US population 6 years of age and older, a single dose of Moderna COVID-19 Vaccine, Bivalent may induce or restore protective immunity against severe COVID-19 caused by currently circulating sublineages of Omicron.

6.3 Effectiveness of Moderna COVID-19 Vaccine, Bivalent in Individuals 6 months through 5 years of age

6.3.1 Inferring effectiveness through immunogenicity of Moderna COVID-19 Vaccine

6.3.1.1 Immunogenicity of Moderna COVID-19 Vaccine Primary Series in Participants 6 Months Through 5 Years of Age

Effectiveness in individuals 6 months through 5 years of age is inferred based on a comparison of immune responses in two subgroups (children 6-23 months, or 2-5 years of age) to adults 18 years through 25 years of age, assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the primary series in participants 6 months through 5 years of age to that following the primary series in participants 18 years through 25 years of age.

Study 4 includes an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind clinical trial component to evaluate the safety, reactogenicity, and effectiveness of Moderna COVID-19 Vaccine in individuals ages 6 months through 5 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection within 2 weeks of study vaccination were excluded from the study. A total of 6,403 participants were randomized 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine (25 µg mRNA per dose) or saline placebo 1 month apart. Participants were followed for occurrence of COVID-19 and safety until 1 year after the last dose.

In Study 4, an analysis was conducted of SARS-CoV-2 neutralizing antibody concentrations and seroresponse rates 28 days after Dose 2 in a subset of individuals 6 months through 5 years of age in Study 4 and participants 18 years through 25 years of age in Study 1 who had no immunologic or virologic evidence of prior SARS-CoV-2 at baseline.

The co-primary immunogenicity analyses consisted of the geometric mean concentration (GMC) ratio [children in the specified age (i.e., children 6-23 months; or 2-5 years of age) to young adults] and the difference in the seroresponse rates (SRRs) (children in the specified age group minus young adults) evaluated against a non-inferiority margin of 10% (LB of the 95% CI ≥−10%) AND a point estimate of difference in SRRs ≥−5% (minimum threshold). Seroresponse was defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥4 × LLOQ, or at least a 4-fold rise if baseline is ≥LLOQ.

In the subgroup of children 2 years through 5 years of age, the GMC ratio was 1.0 (95% CI 0.9, 1.2), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI ≥0.67 and a point estimate of GMC ratio ≥0.8. The difference in SRRs was −0.4% (95% CI −2.7%, 1.5%) which met the pre-specified success criterion of a LL of the 95% CI greater than −10%.

In the subgroup of children 6 months through 23 months of age, the GMC ratio was 1.3 (95% CI 1.1, 1.5), which met the pre-specified success criterion of a lower limit (LL) of the 95% CI ≥0.67 and a point estimate of GMC ratio ≥0.8. The difference in SRRs was 0.7% (95% CI −1.0%, 2.5%), which met the pre-specified success criterion of a LL of the 95% CI greater than −10% and a point estimate greater than −5%.

Noninferior immune responses demonstrated in a comparison of participants 6 months through 5 years of age to participants 18 years through 25 years of age supported the inference of Moderna COVID-19 Vaccine effectiveness in individuals 6 months through 5 years of age.

Please refer to section 4.3 of the EUA Memorandum dated June 16, 2022, for a detailed review of this study.

6.3.1.2 Immunogenicity of Moderna COVID-19 Vaccine Booster Dose Following Moderna COVID-19 Vaccine Primary Series in Participants 17 Months Through 5 Years of Age

Effectiveness of a booster dose of Moderna COVID-19 Vaccine in individuals 6 months through 5 years of age is based on a comparison of immune responses, as assessed by neutralizing antibody concentration against a pseudovirus expressing the SARS-CoV-2 Spike protein from a USA_WA1/2020 isolate carrying the D614G mutation, following the booster dose in study participants 17 months through 5 years of age to that following the primary series in adults 18 years through 25 years of age.

In an open-label study, participants 17 months through 5 years of age received a single booster dose of Moderna COVID-19 Vaccine (10 µg mRNA) at least 6 months after completion of a Moderna COVID-19 Vaccine primary series (two doses 1 month apart). The primary immunogenicity analysis population included 56 booster dose participants in Study 4 and a random subset of 295 participants 18 years through 25 years of age from Study 1 who had completed primary vaccination with two doses of Moderna COVID-19 Vaccine (100 µg mRNA per dose) 1 month apart. Among the 56 participants in the primary immunogenicity analysis population, the median age for receipt of the booster dose was 2.3 years (range 1.4-5.6 years).

The co-primary immunogenicity analyses consisted of the geometric mean concentration (GMC) ratio and the difference in seroresponse rates (SSRs) following the booster dose in participants 17 months through 5 years of age compared to seroresponse rates after the primary series in Study 1 (young adults). Seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series).

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. 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%.

Noninferior immune responses demonstrated in a comparison of participants 17 months through 5 years of age following a booster dose of Moderna COVID-19 Vaccine to participants 18 years through 25 years of age following a two-dose primary series of Moderna COVID-19 Vaccine support the inference of Moderna COVID-19 Vaccine effectiveness after a booster in individuals 6 months through 5 years of age.

Please refer to section 6.3 in the EUA memorandum dated December 7, 2022 for detailed review.

6.3.2 Extrapolation of effectiveness of Moderna COVID-19 Vaccine, Bivalent through immunogenicity

As noted in Section 6.2.2.5 above, vaccine effectiveness of a second booster dose of a bivalent vaccine with an Omicron variant component (Original and Omicron BA.1) was inferred based on the totality of relative immunogenicity data when compared to a second booster dose of Moderna COVID-19 Vaccine. The vaccine effectiveness of a third dose and of a bivalent vaccine with an Omicron variant component in individuals 6 months through 5 years of age is extrapolated from effectiveness in adults (18 years and older).

Please refer to Section 6.2.2.6 above and to section 6.1 of the EUA memorandum dated August 31, 2022 for detailed review.

Based on the totality of the evidence from clinical trials, including efficacy data of the Moderna COVID-19 Vaccine and immunogenicity data of the Moderna COVID-19 Vaccine, and Bivalent Vaccine (Original and Omicron BA.1), it is reasonable to extrapolate from immunogenicity in individuals 5 years of age and older and infer from immunogenicity in individuals 6 months through 5 years of age the effectiveness of Moderna COVID-19 Vaccine, Bivalent in individuals 6 months through 5 years of age.

6.4 Effectiveness of Additional Doses Moderna COVID-19 Vaccine, Bivalent in Individuals ≥65 years of age and older

Waning of vaccine-induced protection against symptomatic disease after an mRNA vaccine booster dose, more modest waning of protection against hospitalization, and additional protection, at least in the short-term, against COVID-19 and COVID-19-associated hospitalization conferred by an additional dose of an mRNA vaccine led to authorization of a second booster dose of the Moderna COVID-19 Vaccine administered following a first booster dose of any FDA authorized or approved COVID-19 vaccine in certain individuals.

Please see EUA Memorandum Dated March 28, 2022 for detailed review.

Based on the totality of the evidence, including evidence described in Section 6.2.2.6 above, it is reasonable to extrapolate from immunogenicity and real-world studies the effectiveness of an additional dose of Moderna COVID-19 Vaccine, Bivalent in individuals 65 years of age and older at least 4 four months after their first dose of a bivalent COVID-19 vaccine.

6.5 Effectiveness of Additional Doses Moderna COVID-19 Vaccine, Bivalent in Immunocompromised Individuals

Additional doses of Moderna COVID-19 Vaccine have previously been authorized in individuals 6 months and older with certain kinds of immunocompromise (i.e., those who have undergone solid organ transplant or who are diagnosed with conditions considered to have an equivalent level of immunocompromise).

Please see EUA Memorandum dated June 16, 2022for detailed review.

6.5.1 Immunogenicity of a Third Primary Series Dose in Individuals with Certain Kinds of Immunocompromise

Safety and effectiveness of the Moderna COVID-19 Vaccine in individuals 6 months through 17 years of age with immunocompromise have been extrapolated from adult data. Safety and effectiveness of a third primary series dose of the Moderna COVID-19 Vaccine were evaluated in an independent study of 60 adults who had had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years) (*Hall VG, Ferreira VH, Ku T et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med 2021 DOI: 10.1056/NEJMc2111462;* NCT04885907). In this study, the adverse event profile a third vaccine dose was similar to that of the second dose and no Grade 3 or Grade 4 events were reported. The administration of a third primary series vaccine dose appears to be only moderately effective in increasing antibody titers.

Please refer to the EUA Review Memorandum dated August 12, 2021 for detailed review.

Based on the totality of evidence, vaccine effectiveness of additional doses of a Moderna COVID-19 Vaccine, Bivalent in certain immunocompromised individuals is extrapolated from Moderna COVID-19 Vaccine effectiveness inferred from immunogenicity evidence in those immunocompromised individuals. Effectiveness of the Moderna COVID-19 Vaccine, Bivalent in certain immunocompromised individuals 6 months of age to 17 years of age have been extrapolated from adult data.

6.6 Safety Data

Please refer to prior FDA review memoranda for detailed review of the safety data from clinical studies supporting the authorization of the Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

The safety of Moderna COVID-19 Vaccine, Bivalent in individuals 6 months of age and older is based on:

- safety data from clinical studies which evaluated primary and booster vaccination with Moderna COVID-19 Vaccine. For detailed review, please refer to section 6 of the following EUA memoranda:
    - EUA Memorandum dated June 16, 2022
    - EUA Memorandum dated October 18, 2021

- safety data from a clinical study which evaluated a booster dose of bivalent vaccine (Original and Omicron BA.1), Please refer to section 6 of the EUA Memorandum dated August 31, 2022

- postmarketing safety data with Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent.

The safety data accrued with the Moderna COVID-19 Vaccine and Moderna's bivalent COVID-19 vaccine (Original and Omicron BA.1) are relevant to Moderna COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

A high-level summary of post marketing safety data is provided below.

Postmarketing Safety Data

Review of post-marketing safety data indicate a similar safety profile of the Original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of April 5, 2023, more than 249 million doses of the original Moderna COVID-19 Vaccine have been administered in the US, including 20,076,974 booster doses of the updated Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Of the total doses of either the Original or Bivalent formulation given in the US, 1,541,532 have been administered to individuals 6 months through 5 years of age and 603,947 have been administered to individuals 6 through 17 years of age, and 247,055,007 doses administered to adults ages 18 years and older (data lock point April 5, 2023). In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain. For important risks identified in the pharmacovigilance plan for Moderna COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/post-marketing studies for the Original Moderna COVID-19 Vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting 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 adverse events of special interest (AESIs) in all ages in the general US population. (Please refer to Section 7 for details).

Taken together, these data informed FDA's assessment of the known and potential benefits and risks of the Moderna COVID-19 Vaccine, and 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, and booster doses of Moderna COVID-19 Vaccine, Bivalent, FDA determined that it was reasonable to extrapolate the available safety data, supporting a favorable benefit-risk balance for use of one vaccine composition (i.e., Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)) and an updated vaccination schedule as: a two-dose series in individuals 6 months through 5 years of age; an additional dose at least 1 month following the most recent dose in individuals 6 months through 5 years of age with certain kinds of immunocompromise who have received two doses (Moderna COVID-19 Vaccine or Moderna COVID-19 Vaccine, Bivalent), and then subsequent, additional doses at the discretion of the healthcare provider; a single dose in individuals 6 years of age and older administered at least 2 months after receipt of a monovalent COVID-19 vaccine; an additional dose at least 4 months following administration of a first bivalent COVID-19 vaccine in individuals >65 years of age; an additional vaccine dose at least 2 months following administration of a prior bivalent COVID-19 vaccine and subsequent doses at the discretion of the healthcare provider in individuals 6 years of age and older with certain kinds of immunocompromise (solid organ transplant recipients and those determined to have a similar level of immunocompromise).

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

7.1 Chemistry Manufacturing and Control (CMC) Information

The two presentations of Moderna COVID-19 Vaccine, Bivalent are noted. The Sponsor did not submit any new CMC/facilities information with this EUA as there are no changes to CMC or facilities.

Multiple-Dose Vials with Dark Blue Caps and Labels with a Gray Border

The Moderna COVID-19 Vaccine, Bivalent in multiple dose vials with dark blue Caps and labels with a Gray Border is supplied as a frozen suspension.

For CMC review, please refer to section 7 of the EUA Memorandum dated August 31, 2022.

Multiple-Dose Vials with Dark Pink Caps and Labels with Yellow Box
The Moderna COVID-19 Vaccine, Bivalent in multiple dose vials with dark pink caps and labels with yellow box is supplied as a frozen suspension.

For CMC review please refer to section 7 of EUA Memorandum dated December 7, 2022

7.2 Clinical Assay Information

Assays used in clinical studies described in Section 6 have been reviewed in previous EUA memoranda. Please refer to Section 6 for the reference to the review memoranda (see also prior FDA review memoranda) for detailed reviews.

7.3 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 has a 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 adults; COVID-19 resulting in hospitalization or death
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine, Bivalent and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The studies below are being conducted for Moderna Covid-19 Vaccine, Original monovalent in large scale databases with an active comparator and will include a sub-analysis for Moderna COVID-19 Vaccine, Bivalent. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Moderna COVID-19 Vaccine, Bivalent in all age groups in the following studies:

  - **Study mRNA-1273-P903.** Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity

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

  - **Study mRNA-1273-P904.** Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe.

    Objective: To assess whether vaccination with Moderna COVID-19 vaccine, including the Bivalent Omicron modified vaccine, is associated with increased rates of AESIs compared with the expected rates overall and stratified by country, sex, and age group.

  - **Study mRNA-1273-P905.** Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries.

Objective: To determine whether exposure to the Moderna COVID-19 vaccine, including the Bivalent Omicron modified vaccine, during pregnancy is associated with an increased risk of:

a) Pregnancy complications
b) Adverse pregnancy outcomes
c) Major congenital malformations in the offspring (overall and organ-specific if feasible)
d) Adverse neonatal outcomes

- **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-P919.** An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Spikevax During Pregnancy.
  Objective: In infants of women exposed to Moderna COVID-19 vaccine, including the Bivalent Omicron modified vaccine, during pregnancy, to assess if there is an associated increase in birth prevalence of major congenital malformations, and adverse neonatal and infant outcomes. In women exposed to vaccine during pregnancy, if there is an associated increased prevalence of hypertensive disorders, gestational diabetes, postpartum hemorrhage, stillbirth, preterm birth, and medically attended spontaneous abortion.

- **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 evaluate the association between the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs, including myocarditis and pericarditis, in all age groups of the general US population for individuals who receive a bivalent booster dose in the US.

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 and adults
- 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.

7.4 EUA Prescribing Information and Fact Sheets

The Full Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), and 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 the consolidated Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), the Dosage and Administration section no longer refers to “primary series” and “booster” doses.

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 of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for over 104 million cases of COVID-19 and over 1.1 million deaths in the US. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. These interventions are generally most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2 they are usually not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19 including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA approved and authorized vaccines provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech and an adjuvanted, protein subunit vaccine from Novavax (in individuals 12 years of age and older only), and the non-replicating viral vector vaccine from Janssen (in certain individual 18 years of age and older only).

The monovalent vaccines were based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of 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, [33, 34] Israel,[21] Qatar,[18] Portugal, [35] and England.[13]

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

and available evidence, vaccination with the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster doses were expected to provoke a stronger immune response and provide better clinical protection against hospitalization to the more recent Omicron subvariants, and evidence from several studies now indicate this to be the case.[22,23,24,25,26,27,28]

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the data from FDA Biologics Effectiveness and Safety (BEST) System, within a week after second dose of mRNA-based COVID-19 vaccine primary series, the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events was 2.1 per 100,000 doses for individuals aged 18–64 years (unpublished data), and 12.5 per 100,000 doses for males aged 18–25 years.[36] 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.[36] The meta-analysis of BEST data for the Pfizer COVID-19 Vaccine reports excess cases per one million second doses for 12–15-year-old males as 132.2 (95%CI: 92.0-189.6), for 16-17-year-old males as 159.9 (95%CI: 59.9-414.3), and for 18-25- year-old males as 95.6 (95%CI: 61.0-147.4). Based on the data from BEST, within a week after the second dose of the Pfizer COVID-19 Vaccine primary series, the crude observed ratio (with adjustment for claims processing delay) of myocarditis or pericarditis was 0.73 cases per 100,000 vaccine doses among individuals aged 5-11 years, and 0.95 cases per 100,000 vaccine doses among male individuals aged 5-11 years (unpublished data, based on fewer than 10 cases). The Moderna COVID-19 Vaccine was authorized in June 2022 for use as a primary series in individuals 6-17 years of age and an equivalent measure for the Moderna COVID-19 Vaccine cannot be estimated at this time due to the insufficient data accumulated with the vaccine in this age group. The myocarditis associated with the administration of mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested 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 additional Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine doses will likely increase the immune response and clinical protection against SARS-CoV-2 variants and may particularly help target the currently predominant Omicron subvariants related to BA.4/BA.5. Administration of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine is appropriate for all individuals 6 months of age and older according to a regimen appropriate for age and vaccination status.

Clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested 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 6 provides a summary of the benefit risk considerations in a standard FDA format.

Table 6. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for nearly 104 million cases and 1.1 million deaths in the US. • There has been a succession of variants (Delta, Omicron BA.1, BA.5. and more recently XBB.1.5, among others) 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 Options for Treatment or Prevention of COVID-19 Disease	• Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity. • There are two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6 months of age and older and bivalent forms of those vaccines are available for use as single booster doses or third primary series dose in individuals 6 months of age and older • An adjuvanted, protein subunit COVID-19 vaccine is authorized for use as a primary series in individuals 12 years of age and older and as a single booster dose for certain individuals 18 years of age and older. • A non-replicating viral vector COVID-19 vaccine authorized for primary vaccination and as a single booster dose in certain individuals 18 years of age and older.	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • Vaccines play an important role in pandemic control and provide important protection.

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. • Studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose provides better protection compared to the monovalent (Original) against symptomatic disease, hospitalization, and death caused by more recently circulating Omicron subvariants.	• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) vaccines provide benefit and may particularly help target the currently circulating Omicron variants. • Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine doses is appropriate for all authorized mRNA COVID-19 vaccine doses to be given in the United States, given the protection compared to the monovalent (Original) that it provides against both original and more recent variant SARS-CoV-2 strains. • Given the prior exposure of most individuals to the virus, the vaccine, or both (hybrid immunity), a single vaccination is appropriate for otherwise healthy individual 5 years of age and older and for those 6 months through 4 years of age who have completed an initial COVID-19 vaccination series. • Such simplification of the vaccination regimen may help facilitate further vaccination efforts and reduce vaccine administration errors in support of public health.

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months of age and older, the known and potential benefits of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered for all doses appropriate to age and any immunocompromise, outweigh the known and potential risks of the vaccine considering the totality of available evidence and the outstanding uncertainties. The benefit-risk profile of available mRNA COVID-19 vaccines is well understood following the administration of over one billion doses. FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. During the recent past when COVID-19 cases have been caused in large part by the BA.5 sublineage and other Omicron subvariants such as XBB.1.5, administration of the bivalent (Original and BA.4/BA.5) COVID-19 vaccine has been demonstrated to have a favorable benefit-risk profile, reducing symptomatic disease, hospitalization, and death, the latter two outcomes being most relevant at this time.

9 Overall Summary and Recommendations

Following review of the EUA request, and VRBPAC recommendations from the January 26, 2023, meeting, the review team considered the following in its assessment of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5):

- As summarized in Section 2 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life- threatening disease or condition.

- The scientific evidence available to support this EUA request includes the following:
    - Clinical safety and effectiveness data following administration of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.1) vaccine,
    - Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.1), and
    - Post-marketing safety surveillance data of the original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.1).
    - Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies.

- Although available evidence suggests that the Original Moderna COVID-19 Vaccine continues to provide protection against serious disease from COVID-19, 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), administered as a single dose to all individuals (unvaccinated or vaccinated) in the United States 6 years of age and older at least 2 months following any prior monovalent COVID-19 vaccine dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- 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), administered as a two dose series to previously unvaccinated individuals 6 months through 5 years of age, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, it is reasonable to conclude that a single dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered to complete a two-dose series in individuals 6 months through 5 years of age who have previously received one dose of the Moderna COVID-19 Vaccine, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, it is reasonable to conclude that a dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered to previously vaccinated individuals 65 years of age and older at least 4 months following a first bivalent COVID-19 vaccine dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- Based on the totality of available scientific evidence, it is reasonable to conclude that an additional 0.25 mL dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered at least 1 month following the most recent dose to individuals 6 months through 5 years of age with certain kinds of immunocompromise who have received two previous doses with Moderna COVID-19 Vaccine or Moderna COVID-19 Vaccine, Bivalent, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5. Based on the

totality of available scientific evidence, it is reasonable to conclude that subsequent additional doses of Moderna COVID-19 Vaccine, Bivalent administered to such individuals at the discretion of the healthcare provider may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5

- Based on the totality of available scientific evidence, it is reasonable to conclude that an additional dose of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), administered at least 2 months following a prior bivalent dose to individuals 6 years of age and older with certain kinds of immunocompromise, and subsequent additional doses administered at the discretion of the healthcare provider, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5 and other Omicron subvariants such as XBB.1.5.
- As summarized in Section 6, effectiveness of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is derived from a combination of clinical studies and real-world evidence.
- 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 the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks when used appropriate to age and immune status for active immunization to prevent COVID-19 caused by SARS-CoV-2 in 6 months of age and older.
- Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variant sublineages BA.4 and BA.5. Uncertainties include those around the level of effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, especially in children, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known and potential risks include generally self-limited common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, and axillary swelling/tenderness) and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Moderna COVID-19 Vaccine recipients. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

Based on the considerations outlined above, the review team recommends removing authorization for emergency use of the monovalent Moderna COVID-19 in the United States and revision of the EUA to provide for use of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered in an appropriate schedule based on age and immune status, as reflected in the Fact Sheets.

10 Appendix A. Adverse Events of Special Interest

Table 7. 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-P203, Appendix 4

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

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

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

Table 8. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

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

Source: Sponsor's Clinical Overview, mRNA-1273-P203, Section 7.5.5.
Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

b Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
c To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d Adler et al 2015.
e Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

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