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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27073, Amendment 644,659
Sponsor	ModernaTX, Inc
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Signatory Authority	David C. Kaslow, M.D., Director, OVRR
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Review Completion Date	September 11, 2023
Established Name/Names used during development	Moderna COVID-19 Vaccine (2023-2024 Formula)
Dosage Forms/Strengths and Route of Administration	A 0.25 mL suspension for intramuscular injection (for 6 months through 11 years of age) (For dosing regimen, dose, and schedule, refer to 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 through 11 years of age

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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 August 16, 2023, SARS-CoV-2 has led to over 770 million cases of coronavirus disease 2019 (COVID-19), including 7 million deaths worldwide, and has caused societal, economic, and healthcare system disruptions. COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19. COVID-19 vaccinations have been estimated to have prevented tens of millions of deaths worldwide in the first year alone after COVID-19 vaccines became available in December 2020.[1]

The Moderna COVID-19 Vaccine (Original monovalent) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the prefusion stabilized full-length spike (S) protein of the Original (Wuhan Hu-1) SARS-COV-2 strain, hereafter referred to as Moderna COVID-19 Vaccine (Original monovalent). The Moderna COVID-19 Vaccine, Bivalent contains mRNAs encoding the prefusion-stabilized S-glycoproteins of Original and SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). For more details on the sequence of authorizations of the Moderna COVID-19 Vaccine (Original monovalent) and the Moderna COVID-19 Vaccine, Bivalent refer to executive summary in FDA Review Memorandum Dated April 18, 2023.

On April 18, 2023, FDA authorized the use of the Moderna and Pfizer-BioNTech bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines in all individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65 years of age and older; and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions resulted in FDA no longer authorizing use of monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) and certain uses of the approved COVID-19 vaccines in the United States (U.S.). For details, refer to FDA Review Memorandum Dated April 18, 2023.

Although real-world effectiveness studies suggest that the current bivalent COVID-19 vaccines continue to provide some protection against other circulating sublineages of Omicron, including XBB.1.5,[2,3] there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time.[3] Additionally, studies indicate that neutralizing antibody titers induced by the current bivalent COVID-19 vaccines against XBB-related sublineages are lower relative to neutralizing antibody titers induced against the matched BA.4/BA.5 sublineage.[4] These data suggest that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. On June 15, 2023, VRBPAC voted to recommend an update of the current COVID-19 vaccine composition to a monovalent XBB-lineage, with preference for the XBB.1.5 sublineage. FDA subsequently advised manufacturers updating their COVID-19 vaccines to develop vaccines with a monovalent XBB.1.5 composition for the 2023-2024 Formula (refer to section 3.2).

As per the April 18, 2023 Emergency Use Authorization (EUA) authorized dosing schedule for Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), individuals 6 through 11 years of age receive a single 25 µg dose, irrespective of prior COVID-19 vaccination status; individuals 6 months to <6 years who have not received any previous doses of a COVID-19 vaccine receive 2 doses (25 µg, each) of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and those in this age group who have received one prior Moderna COVID-19 Vaccine dose receive a single 25 µg dose, and those who have received two prior Moderna COVID-19 Vaccine doses receive a single 10 µg dose.

ModernaTX Inc., on July 18, 2023, requested authorization of their COVID-19 vaccine to include 2023-2024 Formula as a 2-dose series in individuals 6 months to <5 years of age and as a single dose in individuals 5 to <12 years of age (refer to section 5), thereby lowering the age eligibility for receipt of a single-dose regimen, from 6 years to 5 years. Moderna's submission also requested that individuals 6 months through 4 years of age who have received one or more prior doses with Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) receive a single 25 µg dose. The requested revision to the authorized vaccination schedule would provide for individuals 5 years and older with or without prior history of COVID-19 vaccination to receive a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula). The lower age eligibility for receipt of a single dose will also align COVID-19 vaccine pediatric immunization schedules in the U.S., thereby simplifying vaccination schedules and potentially improving vaccine uptake in children. Moderna TX also requested authorization for use of additional doses in individuals with certain kinds of immunocompromise in 6 months through 11 years of age.

Given that the Moderna COVID-19 Vaccine (2023-2024 Formula) is manufactured using the same process as Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), postmarketing safety data for Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) were considered relevant to the safety evaluation of the Moderna COVID-19 Vaccine (2023-2024 Formula). Review of postmarketing safety data indicate a similar safety profile of the Moderna COVID-19 Vaccine (Original monovalent) and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of May 17, 2023, per the Monthly Summary Safety Report, an estimated 774,433,074 doses of the Moderna COVID-19 Vaccine (Original monovalent) and 118,347,825 doses of Moderna COVID-19, Bivalent (Original and Omicron BA.4/BA.5) have been administered to individuals of all ages globally. As of April 5, 2023, more than 230 million Moderna COVID-19 Vaccine (Original monovalent) and 20 million Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) have been administered in the U.S. Of the total doses of Moderna COVID-19 vaccines (Original monovalent and Bivalent) given in the U.S., 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 all doses of Moderna COVID-19 vaccines (Original monovalent and Bivalent) among children 6 months to less than 12 years of age, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were expired product administered, underdose, pyrexia, incorrect dose administered, product administered to patient of inappropriate age, wrong product administered, product storage error, incorrect product formulation administered, vomiting, and inappropriate schedule of product administration. Of the 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 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 post-authorization studies to evaluate the association between the Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to Section 7 for details).

The safety and effectiveness data accrued with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Moderna COVID-19 Vaccine (2023-2024 Formula), because all these vaccines are manufactured using the same process. Evidence to support the safety and effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 5 to <6 years of age, irrespective of prior COVID-19 vaccination status and evidence for safety and effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in previously COVID-19 vaccinated individuals 6 months to < 5 years are discussed in section 6. In addition, the nonclinical data reviewed indicate that Moderna Vaccine (2023-2024 Formula), when used in vaccine naïve or experienced laboratory animals, elicited higher neutralizing antibodies compared with the bivalent vaccine (Original and Omicron BA.4/BA.5) against XBB-related sublineages. Based on the totality of the available evidence (reviewed in detail in sections 6 and 7), it is reasonable to expect that in immunocompetent and immunocompromised individuals 6 months through 11 years of age the Moderna COVID-19 Vaccine (2023-2024 Formula) compared with Moderna COVID-19 Vaccine (Original and Omicron BA.4/BA.5), will likely increase immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages,.

Taken together, the review team recommends: 1) discontinuation of use of the Moderna COVID-19 Vaccine, Bivalent, in the U.S.; and 2) use of age-appropriate doses and dosing schedules of the Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months through 11 years of age, based on previous vaccination status, and immune competence.

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 coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. As of August 16, 2023, SARS-CoV-2 infection has resulted in over 770 million cases of COVID-19 and an estimated 7 million deaths worldwide.[5] Disease symptoms vary. Many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older and individuals with certain co-morbid conditions,[6] may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals.[7] Symptoms associated with SARS-CoV-2 infection in children are similar to those in adults but are generally milder, with fever and cough most commonly reported.[8,9] However, since the January 2022 surge in cases due to Omicron BA.1, rates of COVID-19-associated hospitalizations among infants younger than 6 months old are similar to those of adults ages 65 to 74 years old.[10]

In the U.S., more than 6.3 million COVID-19-associated hospitalizations and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[11] Individuals 65

years of age and older accounted for approximately 14% of cases and 76% of deaths.[12] By contrast, individuals 18 years of age and younger represent 17% of COVID-19 cases and less than 0.3% of deaths.[12] Since the start of the pandemic, 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. COVID-19 vaccines based on the Wuhan-HU-1 strain of SARS-CoV-2 (also referred to as ancestral, reference or original strain) were launched in the U.S, starting in December 2020. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently the Omicron variant of concern. Bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines were deployed in the U.S. starting in September 2022.

The SARS-CoV-2 Omicron variant has continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by post-vaccination (with Original strain vaccines) and post-infection sera compared to the pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from post-vaccination and post-infection antibody responses. By spring 2023, BQ sublineages were rapidly replaced by XBB sublineages, both in the U.S. and globally. The XBB parent lineage resulted from a recombination of BA.2.10.1 and BA.2.75 sublineages, highlighting the relevance of recombination in generating new variants of concern. Recombination can occur during virus replication in cells infected by more than one variant.

XBB sublineages have continued to emerge that have accumulated a small number of mutations in the spike N-terminal domain and the receptor binding domain (RBD). The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world, by April. Compared to the parental XBB lineage virus, XBB.1.5 has two amino acid substitutions, G252V and S486P, in the RBD of the SARS-CoV-2 spike protein. These changes may confer additional growth advantage, likely due in part to increased affinity of the spike protein to the ACE2 receptor conferred by the S486P change.[13] Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5. The XBB.1.9 variant has the same spike protein sequence as XBB.1.5, but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness.[4,14] Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April 2023 the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared with the parental XBB lineage virus, XBB.1.16 has four spike substitutions, i.e., E180V, G252V, K478R, and S486P. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses rose rapidly in many other countries, including the U.S. Preliminary reports have indicated that no further immune evasion result from these substitutions in the XBB.1.16 spike protein compared with XBB.1.5.[15,16] Overall, XBB

sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023; at this time (August 2023), other circulating variants worldwide include XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant variant in the U.S. in late August 2023 was EG.5. EG.5 carries an additional F456L amino acid substitution in the spike protein compared to the parent XBB.1.9.2 subvariant and XBB.1.5. Within the EG.5 lineage, the subvariant EG.5.1 has an additional spike protein substitution Q52H and represents 88% of the available sequences for EG.5 and its descendent lineages.[17]

SARS-CoV-2 evolution is complex and remains unpredictable. Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. Intrinsic viral factors, e.g., mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals. Thus far, the impressive plasticity, especially in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

Two COVID-19 vaccines are currently FDA approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 for use in individuals 12 years of age and older. Three vaccines are currently authorized for use in the U.S. under emergency use authorization (EUA).

2.2.1 Comirnaty (2023-2024 Formula) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Comirnaty (COVID-19 Vaccine, mRNA) (2023-2024 Formula) manufactured by Pfizer for BioNTech, is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty (Original monovalent) contains a mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). 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 currently authorized under EUA for administration of a single dose in individuals 5 years of age and older, three doses in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two doses if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single dose in individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer-BioNTech COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

2.2.2 Spikevax (2023-2024 Formula) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Spikevax (COVID-19 Vaccine, mRNA) (2023-2024 Formula) manufactured by Moderna, is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Spikevax contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized full-length spike (S) protein of

SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is currently authorized under EUA for administration of a single dose in individuals 6 years of age and older, two doses in those individuals 6 months through 5 years of age previously not vaccinated with a COVID-19 vaccine and a single dose in individuals 6 months through 5 years of age previously vaccinated with Moderna COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses of Moderna COVID-19 Vaccine, Bivalent are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

2.2.3 Novavax COVID-19 Vaccine, Adjuvanted

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. For additional information on dosing and schedule, please refer to the Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.4 Therapies for COVID-19

2.2.4.1 FDA-approved therapies for COVID-19

Oral antivirals:
Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), who are:
Hospitalized; or Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Immune modulators:
Olumiant (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra (Tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

2.2.4.2 Emergency use authorized pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19

Oral antivirals:
Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is 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) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression 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 (For detail of previously authorized SARS-CoV-2-targeting monoclonal antibodies, please refer to section 2.2.5 of the FDA Review Memorandum Dated April 18, 2023).

Immune modulators:
Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing 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).

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.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

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

COVID-19 convalescent plasma:
COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

3 Rationale for Strain Change

3.1 Current Effectiveness of Authorized Bivalent COVID-19 Vaccines and Need for a Strain Update

Following emergence of the Omicron variant and its sublineages (BA.1, BA.4/BA.5, and related sublineages) in November 2021, and based on immunogenicity data suggesting improved protection against Omicron sublineages conferred by bivalent COVID-19 vaccines (Original and Omicron BA.1) compared to the original monovalent COVID-19 vaccines, FDA, on August 31, 2022, authorized use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA,5) for booster doses in individuals 18 or 12 years of age and older, respectively, and revised the scope of authorization for these manufacturers' monovalent vaccines to remove their use as a booster dose in those age groups for which a bivalent booster was authorized. Subsequently, FDA also authorized use of the respective bivalent vaccines for booster doses for younger age groups.

Subsequent to the authorizations of the bivalent mRNA COVID-19 vaccines as boosters in children and adults, observational data indicated that the bivalent COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage, compared to the original monovalent vaccines.[18-24] The improved protection against circulating variants provided by the bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines compared with the original monovalent COVID-19 vaccines provided support for the transition to use of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines for all doses for mRNA COVID-19 vaccines authorized in individuals 6 months of age and older as well as support for periodic updates of the strain composition of COVID-19 vaccines. In addition, based on the totality of available scientific evidence, FDA concluded that it was reasonable to expect that bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines administered as a single dose to all individuals (unvaccinated or vaccinated) in the U.S. 5 (Pfizer-BioNTech COVID-19 Vaccine, Bivalent) or 6 (Moderna COVID-19 Vaccine, Bivalent) 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.

In April 2023, FDA authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA,5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for all doses for individuals 6 months of age and older. A single dose regimen of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA,5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized for individuals 5 or 6 years of age and older, respectively. An additional dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA,5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized for individuals 65 years of age and older. Additional doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA,5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) were authorized for individuals with certain kinds of immunocompromise.

SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations (see section 2.1). Although real-world effectiveness studies suggest that the current bivalent vaccines continue to provide protection against circulating sublineages of Omicron, including XBB.1.5,[2,3] there appears to be an inverse relationship between the time since vaccination and

vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time.[3] Additionally, studies indicate that neutralizing antibody titers induced by the current bivalent (Original and Omicron BA.4/BA,5) COVID-19 vaccines against XBB-related sublineages are lower relative to neutralizing antibody titers induced against the matched BA.4/BA.5 sublineage.[4] These data suggest that an updated strain composition of COVID-19 vaccines to match more closely the currently circulating Omicron sublineages is warranted.

3.2 Recommendation for the 2023-2024 Formula of COVID-19 Vaccines in the U.S.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has periodically convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. At the January 26, 2023, VRBPAC meeting on COVID-19 vaccines, FDA stated that it anticipates assessing SARS-CoV-2 evolution at least annually (review of data to commence in the spring of each year) and to convene the VRBPAC in June of each year regarding strain selection for fall vaccination.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the U.S. as of early June 2023. While XBB.1.5 had declined to less than 40% of presumed circulating virus in the U.S., XBB.1.16 was on the rise and XBB.2.3 was slowly increasing in proportion (CDC COVID Data Tracker: Variant Proportions). The trajectory of virus evolution suggested that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolved. Although SARS-CoV-2 continues to evolve, the amino acid sequences of XBB.1.5, XBB.1.16, and XBB.2.3 spike protein appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new amino acid substitutions in the XBB.1.16 spike protein compared to XBB.1.5. By several measures, including escape from antibody neutralization and waning protection, the currently available bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines appear less effective against currently circulating variants (e.g., XBB-lineage viruses) than against previous strains of SARS-CoV-2. The totality of available evidence suggests that an update to the composition of COVID-19 vaccines to a monovalent XBB-lineage vaccine is warranted for 2023–2024.

The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. Sublineages considered by the VRBPAC included XBB.1.5, XBB.1.16, and XBB.2.3. Evidence influencing strain selection discussed by the Committee included virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, pre-clinical immunogenicity studies evaluating immune responses generated by candidate vaccines. The Committee also reviewed manufacturing timelines.

For the 2023-2024 Formula of COVID-19 vaccines in the U.S., the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage. Based on the evidence and other considerations presented, committee members expressed a preference for selection of XBB.1.5 for the 2023-2024 Formula. Based on the totality of the evidence, FDA advised manufacturers seeking to update their COVID-19 vaccines that for the 2023-2024 Formula of COVID-19 vaccines in the U.S. they should develop vaccines with a monovalent XBB.1.5 composition.

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

4.1 U.S. Requirements to Support Issuance of an EUA for a Biological Product

The Secretary of the U.S. 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 U.S. 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 monovalent vaccine to address emerging SARS-CoV-2 variants. With respect to clinical data, the guidance recommends clinical evaluation of modified monovalent vaccines, while also recognizing that FDA's thinking regarding data needed to authorize a modified COVID-19 vaccine may evolve as additional information is accrued with SARS-CoV-2 variants and corresponding vaccines. Although the authorization of Moderna COVID-19 Vaccine (2023-2024 Formula) is not supported by clinical studies of the 2023-2024 Formula vaccine, FDA's thinking about the need for such data has evolved since issuance of the guidance. Based upon the accumulated evidence and experience with the Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5) (see Section

6), it is reasonable to conclude that clinical studies of the Moderna COVID-19 Vaccine (2023-2024 Formula) are not necessary to support issuance of an EUA. The experience with the Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5), combined with the CMC and preclinical data submitted as part of the EUA request, support a favorable benefit-risk profile for the uses of Moderna COVID-19 Vaccine (2023-2024 Formula) that are under consideration.

5 EUA Amendment Request to Include the 2023-2024 Formula for Moderna COVID-19 Vaccine

5.1 Summary of the EUA Request

Following the June 15, 2023, VRBPAC discussion and FDA's advice to manufacturers updating their vaccines to develop vaccines with a monovalent XBB.1.5 composition (section 3.2). ModernaTX Inc., on July 18, 2023, requested authorization of their COVID-19 Vaccine to include the 2023-2024 Formula vaccine as a 2-dose series in individuals 6 months to <5 years of age and as a single dose in individuals 5 to <12 years of age (refer to section 5), thereby lowering the age eligibility for receipt of a single dose, from 6 years to 5 years of age. Moderna's submission also requested that individuals 6 months through 4 years of age, who have received one or more prior Moderna COVID-19 vaccine doses, receive a single 25 µg dose. Moderna's request included the following information:

- Preclinical data that support the strain selection
- CMC Information supporting the Moderna COVID-19 Vaccine (2023-2024 Formula) provided in Module 3 of the EUA request.
- Clinical overview that supported the revised dose and dosing regimen

The request includes an update to the dose and administration schedule for Moderna COVID-19 Vaccine (2023-2024 Formula), consistent with the following tables.

Table 1. Individuals 6 Months Through 4 Years of Age by Moderna COVID-19 Vaccination Status

Number of Previous Doses of Moderna COVID-19 Vaccine(s)[a]	Moderna COVID-19 Vaccine (2023-2024 Formula) Dosing Regimen, Dose and Schedule[b]
0[c]	2 doses,[d] 0.25 mL each Dose 1: month 0 Dose 2: month 1
1	Single Dose, 0.25 mL One month after receipt of a previous dose of Moderna COVID-19 vaccine[a]
≥2	Single dose, 0.25 mL ≥2 months after receipt of the last previous dose of Moderna COVID-19 vaccine[a]

a. Previous dose(s) of Moderna COVID-19 vaccine(s) refers to Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
b. For individuals with certain kinds of immunocompromise previously vaccinated with a Moderna COVID-19 vaccine, see text following the tables for dosing information.
c. Not previously vaccinated with any COVID-19 vaccine.
d. Individuals turning from 4 years to 5 years of age during the vaccination series should receive both doses with Moderna COVID-19 Vaccine (2023-2024 Formula).

Table 2. Individuals 5 Years Through 11 Years of Age Irrespective of COVID-19 Vaccination Status

Moderna COVID-19 Vaccine (2023-2024 Formula) Dosing Regimen, Dose and Schedule[a]
Single dose, 0.25 mL If previously vaccinated, ≥2 months after receipt of the last previous dose of COVID-19 vaccine[a,b]

a. For individuals with certain kinds of immunocompromise, see text below tables for further dosing information.
b. COVID-19 vaccine refers to the monovalent COVID-19 vaccines that encode the spike protein of the original SARS-CoV-2 and the bivalent COVID-19 vaccines encoding the spike protein of original SARS-CoV-2 and of the Omicron variant lineages BA.4 and BA.5.

Dosing Schedule for Immunocompromised

Individuals with certain kinds of immunocompromise[a] 6 months through 11 years of age should complete at least a three-dose series with a COVID-19 vaccine, each dose one month apart.[b] At least 1 dose should be with a COVID-19 vaccine (2023-2024 Formula).

- If previously not vaccinated, complete the three-dose series with Moderna COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with one or two dose(s) of Moderna COVID-19 Vaccine (Original monovalent) and/or the Moderna COVID-19 Vaccine Bivalent, complete the remaining dose(s) in the three-dose series with Moderna COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with three or more doses, administer a single dose of Moderna COVID-19 Vaccine (2023-2024 Formula) at least two months following the last previous dose.[c,d]

An additional dose of Moderna COVID-19 Vaccine (2023-2024 Formula) may be administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula).[e,f] Additional doses of Moderna COVID-19 Vaccine (2023-2024 Formula) may be administered at the discretion of the healthcare provider. Taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.

5.2 FDA's Approach for Selection of Strains to be Included in 2023-2024 Formula for COVID-19 Vaccines

In previous discussions with the VRBPAC, FDA described the proposed evidentiary basis that would be used to determine the need for updating the strain composition of COVID-19 vaccines. The relevant data reviewed would ideally include multiple types and sources. FDA reviewed various types of data as listed below, engaged with the key partners generating such data, including vaccine manufacturers and other U.S. government agencies, and reviewed the

[a] Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.
[b] COVID-19 vaccine, each dose of the three-doses series given one month apart, refers to Moderna COVID-19 vaccines. Individuals turning from 11 to 12 years of age during the vaccination series may complete the series with doses of Moderna COVID-19 Vaccine (2023-2024 Formula).
[c] For immunocompromised individuals 6 months through 4 years of age, the last previous dose refers to the last dose of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent which are no longer authorized for use in the U.S.
[d] For immunocompromised individuals 5 years through 11 years of age, the last previous dose refers to the last dose of a COVID-19 vaccine (Original monovalent) or bivalent COVID-19 vaccine which are no longer authorized for use in the U.S.
[e] For immunocompromised individuals 6 months through 4 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Moderna COVID-19 Vaccine (2023-2024 Formula).
[f] For immunocompromised individuals 5 years through 11 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) or Moderna COVID-19 Vaccine (2023-2024 Formula).

discussions and recommendations by other regulatory groups and public health agencies related to COVID-19 vaccine strain composition for 2023-2024.

- **Virus surveillance and genomic analyses to identify emerging new virus variants**. As described in section 2.1, SARS-CoV-2 XBB-lineage viruses currently predominate in the U.S. and globally.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses**. As described in section 2.1, SARS-CoV-2 XBB-lineage viruses have numerous amino acid changes relative to previously circulating SARS-CoV-2 viruses and the strains used in the authorized bivalent COVID-19 vaccines, suggesting continued evolution and increasing immunological distance from the Omicron BA.4/BA.5 component of currently authorized COVID-19 mRNA vaccines.
- **Post-vaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants such as XBB-lineage viruses**. Since COVID-19 vaccine manufacturers are best positioned to generate the robust data needed from post-vaccination human serology studies, FDA set up informal technical working group meetings with each of the manufacturers of currently authorized/approved COVID-19 vaccines to share and discuss findings from human serology studies of their current vaccines against current circulating viruses. These data were presented at the June 2023 VRBPAC by the vaccine manufacturers.
- **Pre-clinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant spike components) against antigenically distinct circulating virus variants**. Pre-clinical immunogenicity data (neutralizing antibody) can provide an indication of how well antibodies to the spike protein of one strain will cross-neutralize other variant strains of SARS-CoV-2. These data help inform strain selection in combination with other data. As with human serology studies, COVID-19 vaccine manufacturers are also able to generate pre-clinical immunogenicity studies with new candidate vaccines and each of the manufacturers of authorized/approved COVID-19 vaccines has produced several candidate vaccines at risk and evaluated them in pre-clinical studies. These data were also presented at the June 2023 VRBPAC by the vaccine manufacturers.

5.3 Basis for EUA Revision to Remove Authorization for Use of Moderna COVID-19 Vaccine, Bivalent in the U.S. and Clarify Export and Other 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).

Circumstances currently exist that make it appropriate a revision of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) EUA to protect the public health. As outlined in Section 2.2, the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) is authorized for use in individuals 6 months of age and older. Authorization of the Moderna COVID-19 Vaccine (2023-2024 Formula), for individuals 6 months through 11 years of age, as described in the EUA request, is being considered for the express purpose of improving protection against the currently circulating SARS-CoV-2 Omicron sublineages, resulting in a more favorable anticipated benefit/risk profile for the Moderna COVID-19 Vaccine (2023-2024 Formula). FDA has also approved a supplemental biologics license application for Spikevax (2023-2024 Formula), which contains mRNA encoding the viral spike (S) glycoprotein of

Omicron XBB.1.5, for active immunization to prevent COVID-19 in individuals 12 years of age and older. In addition, revising the EUA to remove the authorization of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) use in the U.S. ensures that vaccination programs will continue to use a single current formula (i.e., 2023-2024 Formula) for Moderna's COVID-19 vaccines, which should continue to help minimize vaccine administration errors that would result from availability of multiple different vaccine formulas and also potentially encourage vaccine uptake. Consequently, at this time, revising the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) EUA to remove its authorization for use in the U.S. is appropriate to protect the public health.

That said, the considerations about the U.S. vaccination programs are not applicable when the vaccine is used in other countries, and existing supplies of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) 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, Bivalent is currently authorized. Therefore, it is appropriate to continue to authorize the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) for export.

Accordingly, authorization of the Moderna COVID-19 Vaccine (2023-2024 Formula) for use in individuals 6 months through 11 years of age as described in the EUA request, would be accompanied by the revision of the authorization for the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to remove its authorization for use in the U.S. in all age groups 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, Bivalent (Original and Omicron BA.4/BA.5) and associated Fact Sheets are no longer authorized for use in the U.S. 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.

Previously, FDA's EUA required the distribution of the Moderna COVID-19 vaccines to emergency response stakeholders at the direction of the U.S. government as a condition necessary or appropriate to protect the public health. Due to changed circumstances, we conclude that this limitation on distribution is no longer necessary or appropriate to protect the public health. Whereas there was previously a need for the U.S. government to coordinate distribution across federal, state and local government entities to ensure appropriate allocation of the vaccines, this is no longer the case. In addition, we are no longer requiring all vaccination providers administering COVID-19 vaccine to be enrolled in the CDC COVID-19 Vaccination Program, as CDC no longer plans for that program to apply to all vaccination providers and this requirement is no longer necessary or appropriate to protect the public health.

6 FDA Review of Clinical Effectiveness and Safety Data

6.1 Overview of Clinical Studies

The effectiveness data accrued with the Moderna COVID-19 Vaccine (Original monovalent) (no longer authorized for use in the U. S.) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Moderna COVID-19 Vaccine, (2023-2024 Formula),

because these vaccines are manufactured using the same process. A high-level summary of previously reviewed data that support the effectiveness of Moderna COVID-19 Vaccine (2023-2024 Formula) for individuals 6 months through 11 years of age is provided below.

6.1.1 Effectiveness of Moderna COVID-19 Vaccine (2023-2024 Formula)

The effectiveness of Moderna COVID-19 Vaccine (2023-2024 Formula) for individuals 6 months through 11 years of age is based on:

- Effectiveness of Moderna COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older, and
- Immunogenicity of the bivalent vaccine (Original and Omicron BA.1) in individuals 18 years of age and older,

based on the following evidence (for detailed review of the evidence, please refer to section 6.2 and 6.3 of the FDA Review Memorandum Dated April 18, 2023):

- Efficacy of Two-Dose Primary Series of Moderna COVID-19 Vaccine (Original monovalent) in Participants 18 Years of Age and Older
- Effectiveness of Two-Dose Primary Series of Moderna COVID-19 Vaccine (Original monovalent) in Participants 12 Years Through 17 Years of Age
- Effectiveness of Two-Dose Primary Series of Moderna COVID-19 Vaccine (Original monovalent) in Participants 6 Years Through 11 Years of Age
- Effectiveness of Two-Dose Primary Series of Moderna COVID-19 Vaccine (Original monovalent) in Participants 6 Months Through 5 Years of Age
- Immunogenicity of Moderna COVID-19 Vaccine (Original monovalent) Booster Dose Following Moderna COVID-19 Vaccine Primary Series in Participants 6 Years Through 11 Years of Age
- Immunogenicity of Moderna COVID-19 Vaccine (Original monovalent) Booster Dose Following Moderna COVID-19 Vaccine Primary Series in Participants 17 Months Through 5 Years of Age
- Immunogenicity of Bivalent Vaccine (Original and Omicron BA.1) Administered as a Second Booster Dose in Participants 18 Years of Age and Older
- Immunogenicity of the Moderna COVID-19 Vaccine Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (for detailed review of the evidence, please refer to FDA Review Memorandum Addendum Dated November 18, 2021)
- Immunogenicity of a Single Dose of Moderna COVID 19 Vaccine (Original monovalent), in Participants 6 years of Age and Older with Evidence of Prior SARS-CoV-2 Infection

Evidence to support the effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 5 to <6 years of age, irrespective of prior COVID-19 vaccination status, was reviewed previously to support the effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 years of age and older (see section 6.2 FDA Review Memorandum Dated April 18, 2023), and is primarily based on the high seroprevalence rate among individuals 5 years of age and older in the U.S. It is anticipated that a 5-year-old and a 6-year-old would have similar prior SARS-CoV-2 exposure (e.g., school), and thus, comparable levels of pre-existing SARS-CoV-2 immunity. Based on the available evidence it is reasonable to expect that a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) will elicit comparable immune responses and have

comparable effectiveness in an individual 5 years of age, as it would in an individual 6 years of age.

The effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months to < 5 years previously vaccinated with Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is based on the effectiveness of a 10 µg dose of Moderna COVID-19 Vaccine (Original monovalent) in participants 17 months to <6 years in Study P204 who previously received a 2-dose series (25 µg, 1 month apart) of Moderna COVID-19 Vaccine. These data were previously reviewed under EUA memorandum dated December 2, 2022. Based on the available evidence, it is reasonable to expect that a 25µg dose would induce equivalent, if not more robust immune responses as those elicited by the 10µg dose evaluated in Study P204, given the higher antigenic dose-level.

6.1.2 Immunocompromised Individuals

The effectiveness of Moderna COVID-19 Vaccine (2023-2024 Formula) three-dose series in individuals 6 months through 11 years of age with certain kinds of immunocompromise is inferred from immunogenicity of a third primary series dose in Individuals with certain kinds of immunocompromise (For detailed review of the evidence, please refer to FDA Review Memorandum Dated August 12, 2021).

The effectiveness of additional doses of Moderna COVID-19 Vaccine (2023-2024 Formula) for immunocompromised individuals 6 months through 11 years of age is inferred from the following evidence (for detailed review of the evidence, please refer to sections of the FDA Review Memorandum Dated April 18, 2023 listed below):

- Immunogenicity of Moderna COVID-19 Vaccine Booster Dose Following Moderna COVID-19 Vaccine (Original monovalent) Primary Series in Participants 6 Through 11 Years of Age (For detailed review of the evidence, please refer to section 6.2.2.5 of FDA Review Memorandum Dated April 18, 2023)
- Immunogenicity of Moderna COVID-19 Vaccine (Original monovalent) Booster Dose Following Moderna COVID-19 Vaccine (Original monovalent) Primary Series in Participants 17 Months Through 5 Years of Age (For detailed review of the evidence, please refer to section 6.3.1.2 of FDA Review Memorandum Dated April 18, 2023)
- Effectiveness of Additional Doses Moderna COVID-19 Vaccine, Bivalent in Immunocompromised Individuals (For detailed review of the evidence, please refer to section 6.5 of FDA Review Memorandum Dated April 18, 2023)

6.1.3 Conclusion

The effectiveness data accrued with the Moderna COVID-19 Vaccine (Original monovalent) (no longer authorized for use in the U.S.) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Moderna Vaccine, (2023-2024 Formula) because these vaccines are manufactured using the same process. The effectiveness of Moderna COVID-19 Vaccine (2023-2024 Formula) is based on the totality of evidence from clinical trials, including efficacy and effectiveness data with the Moderna COVID-19 Vaccine (Original monovalent) and immunogenicity data with a bivalent vaccine (Original and Omicron BA.1). It is reasonable to expect, from extrapolation of immunogenicity in individuals 5 years of age and older and from inference of efficacy and immunogenicity in individuals 6 months through 4 years of age that Moderna COVID-19 Vaccine (2023-2024 Formula) may be effective in individuals 6 months through 11 years of age. In addition, preclinical data demonstrate that, when compared with the

Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Moderna COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against currently circulating XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.

Consequently, to address the urgent public health need for COVID-19 vaccine more closely matched to circulating variants, FDA considers it appropriate to issue an EUA for the Moderna COVID-19 Vaccine (2023-2024 Formula) based on relevant safety and effectiveness evidence from previously authorized and currently authorized or approved Moderna COVID-19 vaccines manufactured using the same process, in addition to supportive pre-clinical animal data for the Moderna COVID-19 Vaccine (2023-2024 Formula).

6.2 Safety Data

Please refer to prior FDA review memoranda for detailed review of the safety data from clinical studies that supported the authorization of the Moderna COVID-19 vaccines.

The safety of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months through 11 years of age is based on:

- Safety data from clinical studies which evaluated primary and booster vaccination with Moderna COVID-19 Vaccine (Original monovalent). 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 pertaining to additional safety follow up were also reviewed in support of this EUA. For detailed review of this follow-up data please refer to the clinical memorandum supporting the approval of STN 125752/68.

- 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 (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent.

The safety data accrued with the Moderna COVID-19 Vaccine (Original monovalent) and the bivalent vaccine (Original and Omicron BA.1) are relevant to Moderna COVID-19 Vaccine (2023-2024 Formula) because these vaccines are manufactured using the same process.

Evidence to support the safety of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in COVID-19 vaccine naïve individuals 5 to <6 years of age consist of safety data obtained from the study of a 2-dose series (25 µg, 1 month apart) of Moderna COVID-19 Vaccine (Original monovalent) in COVID-19 vaccine naïve participants 6 months to <6 years of age in Study P204 (reviewed in EUA memorandum dated June 16, 2022). In this study, a 25-µg dose of the vaccine had an acceptable safety profile after Dose 1 and after Dose 2. Evidence to support the safety of a single 25-µg dose of Moderna COVID-19 Vaccine (2023-2024) in individuals 5 to <6 years of age who have previously received 2 or more doses of Moderna COVID-19 vaccines can be inferred based on the safety data after a 2-dose series of Moderna

COVID-19 Vaccine (Original monovalent) in participants 6 months to < 6 years with evidence of prior SARS-CoV-2 infection, and will be further discussed in the section below.

The safety of a single 25-µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in previously COVID-19 vaccinated individuals 6 months to <5 years can be inferred based on the safety of a 2-dose series (25 µg, 1 month apart) of Moderna COVID-19 Vaccine (Original monovalent) in participants 6 months to <6 years in Study P204 with evidence of prior SARS-CoV-2 infection (reviewed in EUA memorandum dated June 16, 2022). As shown in Tables 68 and 91 of the EUA memorandum dated June 16, 2022, solicited adverse reactions (ARs) after Dose 1 in participants who had evidence of prior SARS-CoV-2 infection (baseline SARS-CoV-2 positive) were generally reported at higher rates compared to those reported after Dose 1 in participants who had no evidence of prior SARS-CoV-2 infection (baseline SARS-CoV-2 negative). In the baseline SARS-CoV-2 positive participants, rates of solicited ARs after Dose 1 were comparable with those reported after Dose 2, in baseline SARS-CoV-2 negative participants. These findings suggest that the natural infection in baseline SARS-CoV-2 positive participants mimic Dose 1 of the vaccine in baseline SARS-CoV-2 negative participants, and thus it is reasonable to expect that the safety profile post-Dose 2 in baseline SARS-CoV-2 positive participants may be similar to what can be expected after a third or additional 25-µg dose of the vaccine in individuals who have previously received 2 or more doses of a Moderna COVID-19 vaccine. In real world settings, Moderna COVID-19 Vaccine (2023-2024 Formula) may often be administered at a much longer time interval after the last COVID-19 vaccine dose; therefore, the reactogenicity after a 25-µg dose in previously vaccinated individuals 6 months to <5 years is expected to be less than what was observed following Dose 2 in a two-dose series with one month interval in Study P204. Based on the available data, it can be inferred that a single 25-µg dose in individuals 6 months to <5 years, who have previously received 2 or more doses of a Moderna COVID-19 vaccine, is expected to have an acceptable safety profile.

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

6.2.1 Postmarketing Safety

Review of postmarketing safety data indicate a similar safety profile of the Moderna COVID-19 Vaccine (Original monovalent) and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). As of May 17, 2023, per the Monthly Summary Safety Report, an estimated 774,433,074 doses of the Moderna COVID-19 Vaccine, Original and 118,347,825 doses of Moderna COVID-19, Bivalent have been administered to individuals of all ages globally. As of April 5, 2023, more than 230 million doses of Moderna COVID-19 Vaccine (Original monovalent) and 20 million doses of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) have been administered in the U.S. Of the total doses of either the Original or Bivalent formulation given in the U.S., 1,541,532 have been administered to individuals 6 months through 5 years of age, 603,947 have been administered to individuals 6 through 17 years of age, and 247,055,007 have been administered to adults ages 18 years and older (data lock point April 5, 2023)

In recipients of all doses of Moderna COVID-19 vaccines (Original and Bivalent) among children 6 months to less than 12 years of age, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were expired product administered, underdose, pyrexia, incorrect dose administered, product administered to patient of inappropriate age, wrong product administered, product storage error, incorrect product formulation administered, vomiting, and inappropriate schedule of product administration.

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 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 post-authorization studies to evaluate the association between the Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to Section 7 for details).

Taken together, these data informed FDA's assessment of the known and potential benefits and risks of Moderna COVID-19 Vaccine (2023-2024 Formula). Based upon the accumulated experience with all doses of Moderna COVID-19 vaccines to date, FDA determined that it was reasonable to extrapolate the available safety data, supporting a favorable benefit-risk profile for use of the 2023-2024 Formula of the Moderna COVID-19 Vaccine and the proposed updated vaccination schedule.

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

7.1 Chemistry Manufacturing and Control (CMC) Information

The Moderna COVID-19 vaccine (Code number mRNA-1273) consists of a nucleoside-modified messenger RNA (mRNA) encapsulated in a lipid nanoparticle (LNP). The mRNA encodes the full-length spike (S) glycoprotein of SARS-CoV-2 stabilized in the pre-fusion conformation.

The 2023-2024 Formula of the Moderna COVID-19 Vaccine (Code number mRNA-1273.815) for use in individuals 6 months through 11 years of age is supplied as a (b) (4) fill presentation (0.1 mg mg/mL mRNA) provided as a sterile white to off-white suspension in a single-dose vial with a dark blue cap and a label with a green box. Each 0.25 mL dose contains 25 ug mRNA encoding the Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5 (mRNA code CX-038839). Each dose also contains the following ingredients: a total lipid content of 0.5 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.13 mg tromethamine, 0.62 mg tromethamine hydrochloride, 0.011 mg acetic acid, 0.049 mg sodium acetate trihydrate, and 21.8 mg sucrose.

The manufacturing process for the drug substance (DS) consists of (b) (4) . The mRNA-1273 drug product (DP) is manufactured by adjusting the (b) (4) filling of final containers and labeling/packaging. The DS manufacturing and controls for variant vaccines are the same as used for the authorized prototype vaccine, except for the (b) (4) . The DS manufacturing processes and controls were reviewed under the original EUA submission and were adequately characterized and qualified.

The major DP change consists of the use of a single-dose vial presentation, which will replace the multidose vial, and the addition of new manufacturing sites. To support this EUA amendment, process-performance qualification (PPQ) data and in-process, release, and characterization data for three DP lots were provided for each DP manufacturing site (Patheon Manufacturing Services, LLC, Greenville, NC, and Catalent Anagni S.r.l, Anagni, Italy). The DP manufacturing processes and controls were adequately characterized and qualified. Once

authorized, Moderna will submit the Certificates of Analysis (CoAs) of DP lots to be distributed under EUA for FDA review at least 48 hours prior to lot distribution.

The analytical procedures developed and used for the release and stability monitoring of the DS and DP include tests to ensure vaccine safety, identity, purity, quality, and potency. All non-compendial analytical procedures have been validated. The validation results demonstrate acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the quality control of DS and DP.

Stability studies with monovalent and bivalent DP formulations containing mRNAs for different Spike variants support the proposed DP long-term storage conditions of 12 months at -50°C to -15°C, which may include storage at 2°C to 8°C for up to 30 days and 8°C to 25°C for 24 hours. All DS and DP stability studies of SARS-CoV-2 Omicron variant lineage XBB.1.5 are ongoing and will continue to be monitored. Stability data will be submitted to the EUA as they become available.

7.2 Facilities

The manufacture of the Moderna COVID-19 Vaccine (2023-2024 Formula) single-dose presentation in (b) (4) vials for the pediatric doses is performed at Catalent Anagni S.r.l (FEI: 3002806546) and Patheon Manufacturing Services (FEI: 1018495) facilities. The review of the facilities and manufacture supporting the amended EUA is documented under STN 125752/74 and STN 125752/68.

FDA finds that all facilities within the scope of this authorization for the Moderna COVID-19 Vaccine (2023-2024 Formula) single-dose presentation in (b) (4) vials for the pediatric doses, are adequate to support its use under an EUA.

7.3 Nonclinical Studies

Immunogenicity of the Moderna COVID-19 Vaccine (2023-2024 Formula) has been evaluated in mice. The vaccine was tested in both naïve mice as a two-dose primary series and mRNA-1273 vaccine-experienced mice as a booster dose. When compared with the bivalent (Original and Omicron BA.4/BA.5) vaccine, Moderna COVID-19 Vaccine (2023-2024 Formula) vaccine induced higher binding and neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, and XBB.2.3. These data are therefore considered supportive for the strain change to Omicron XBB.1.5 sublineage for the Moderna COVID-19 Vaccine (2023-2024).

7.4 Pharmacovigilance Activities

Moderna is conducting safety-related post-authorization/postmarketing studies for the original monovalent and bivalent (Original and Omicron BA.4/BA.5) vaccines, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Moderna has a pharmacovigilance plan (version 7.2) to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine (2023-2024 Formula). 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
- Missing Information: Use in pregnancy and while breast-feeding, long-term safety, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with

unstable health conditions and co-morbidities, and use in subjects with autoimmune or inflammatory disorders

7.4.1 Sponsor Pharmacovigilance Activities

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Moderna COVID-19 Vaccine (2023-2024 Formula) 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); 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; newly identified safety concerns; and cumulative and interval doses distributed. The EUA Letter of Authorization will be revised from a required monthly submission of periodic safety reports to require such reports monthly or at another appropriate reporting interval determined by the Office of Biostatistics and Pharmacovigilance. This change will provide flexibility to modify the reporting interval in the future, if appropriate given the extensive global safety database and the continued accumulation of extensive postmarketing safety data on Moderna's COVID-19 vaccines.
- Post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine (2023-2024 Formula) 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 (2023-2024 Formula). This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Moderna COVID-19 Vaccine (2023-2024 Formula) in all age groups in the following studies:
    - **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 all Moderna COVID-19 vaccine, including the 2023-2024 vaccine, if feasible.

    - **Study mRNA-1273-P910.** Clinical Course, outcomes, and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2

      Objectives:
      1) To identify possible risk factors for myocarditis and pericarditis following Moderna vaccination targeting SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics.
      2) To characterize the clinical course of myocarditis and pericarditis of varying original, including myocarditis and pericarditis associated with and without Moderna vaccination targeting SARS-CoV-2 and to

identify prognostic factors in the course of myocarditis and pericarditis.

- **Study mRNA-1273-P920.** Postmarketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the U.S. This study will include all Moderna vaccines targeting SARS-CoV-2 in the current protocol, including Moderna COVID-19 Vaccine (2023-2024 Formula)

  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 U.S. population for individuals who receive a bivalent booster dose in the U.S. This study will now contain an analysis of all Moderna vaccines targeting SARS-CoV-2 in the current protocol, including Moderna COVID-19 Vaccine (2023-2024 Formula).

7.4.2 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
- Cases of COVID-19 that result in hospitalization or death

Additionally, potential vaccination errors are mitigated through coloration of the vial caps and borders, information in the label, and available education materials for Healthcare Providers.

7.5 EUA Prescribing Information and Fact Sheets

The 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.

8 Benefit/Risk in the Context of the Proposed EUA for Moderna COVID-19 Vaccine (2023-2024 Formula) 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 U.S. Since the start of the pandemic, there has been a succession of SARS-CoV-2 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 generally not effective for individuals with 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 may 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).

The original monovalent vaccines were based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. Vaccine effectiveness against symptomatic disease declined more rapidly than that against serious disease, as illustrated by studies conducted in the U.S.,[25,26] Israel,[27] Qatar,[28] Portugal,[29] and England.[30] In the setting of the viral variants that have emerged in the past, booster doses with available vaccines (based on the ancestral strain) were able to restore some degree of protection against serious and symptomatic disease.

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have been evaluated by both Moderna and Pfizer- BioNTech. However, these booster vaccines were not deployed in the U.S. due to the rapid evolution of the SARS-CoV-2 variants. Following emergence of the Omicron variant and its sublineages (BA.4/BA.5 and related sublineages) in November 2021, and based on data suggesting improved protection against Omicron sublineages conferred by the bivalent vaccines [Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5); Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)]compared to the monovalent vaccines [Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine (Original monovalent)]. FDA, on August 31, 2022, authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for booster doses in individuals 12 or 18 years of age and older, respectively. In April 2023, the FDA authorized the use of the bivalent COVID-19 vaccines for all doses in individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65 years of age and older; and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.

Bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage compared with the original monovalent COVID-19 vaccines. However, the effectiveness of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines against Omicron sublineages, including the most recently circulating sublineages, appears to wane over time (refer to section 3.1), suggesting that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted.

The safety and effectiveness data accrued with Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent are relevant to Moderna COVID-19 Vaccine (2023-2024 Formula), because all these vaccines are manufactured using the same process. Evidence to support the safety and effectiveness of a single 25 µg dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 5 to <6 years of age, irrespective of prior COVID-19 vaccination status and evidence for safety and effectiveness of a single 25 µg dose

of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals previously vaccinated with Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in 6 months to < 5 years is discussed in section 6. In addition, the nonclinical data reviewed indicate that Moderna COVID-19 Vaccine (2023-2024 Formula), when administered to vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared with the bivalent vaccine (Original and Omicron BA.4/BA.5) against currently circulating XBB-related sublineages. Based on the totality of the available evidence (reviewed in detail in sections 6 and 7), it is reasonable to expect in immunocompetent and immunocompromised individuals 6 months through 11 years of age that the Moderna COVID-19 Vaccine (2023-2024 Formula) will likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the currently predominant Omicron sublineages, compared to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

Additional doses may be associated with transient local and systemic symptoms similar to those seen previously with Moderna COVID-19 vaccines. 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.[30] 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. The meta-analysis of BEST data for the Pfizer-BioNTech 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 used to continuously monitor adverse reactions and any emerging safety concerns post EUA.

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 used to assess whether any new safety concerns emerge. Table 3 provides a summary of the benefit-risk considerations in a standard FDA format.

Table 3. 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 U.S. • 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 bivalent 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. • Original monovalent mRNA-based COVID-19 vaccines authorized in the U.S. initially had high effectiveness (90-95%) against symptomatic disease; however, in combination with waning individual immunity, vaccine effectiveness declined with the emergence of the now dominant Omicron variant; this effect is most prominently observed in older individuals; 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. • Currently, there are two authorized bivalent mRNA COVID-19 vaccines for use in the U.S. as a two or three dose series in 6 months through 4 or 5 years of age and as a single dose in 5 or 6 years 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.	• 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) • COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19.

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 U.S. because of SARS- CoV-2 variant evolution. • Preclinical data demonstrating that Moderna COVID-19 vaccine (2023-2024 Formula) when used in vaccine naïve and vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to the bivalent vaccine (Original and Omicron BA.4/BA.5) against currently circulating XBB-related sublineages. • Residual uncertainty remains in how the magnitude of the expected increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease	• The totality of the available evidence indicates it is reasonable to expect that Moderna COVID-19 Vaccine (2023-2024 Formula) may provide benefit and may particularly help target the currently circulating XBB sublineages. • Given the enhanced neutralizing antibody activity against more recently circulating SARS-CoV-2 variants demonstrated in nonclinical studies of Moderna COVID-19 Vaccine (2023-2024 Formula) compared with the current bivalent (Original and Omicron BA.4/BA.5), it is reasonable to expect that administration Moderna COVID-19 Vaccine (2023-2024 Formula) doses may provide additional benefit compared with administration of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months through 11 years of age, the known and potential benefits of the Moderna COVID-19 Vaccine (2023-2024 Formula) outweigh the known and potential risks of the vaccine when used as described in section 5.1 for all doses appropriate to age and immunocompromise, 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 worldwide. FDA's previous benefit-risk assessments, based in part on real-world evidence that clearly demonstrated the benefits of available COVID-19 vaccines, concluded that benefits outweighed risks (please refer to section 8 of FDA Review Memorandum Dated April 18, 2023). During the current wave of COVID-19 caused in large part by the XBB-related sublineages, administration of a Moderna COVID-19 Vaccine (2023-2024 Formula) is expected to have a favorable benefit-risk profile and to restore protection against serious outcomes from COVID-19.

9 Overall Summary and Recommendations

Following review of the EUA request, and VRBPAC recommendations from the June 15, 2023, meeting, the review team considered the following in its assessment of the Moderna COVID-19 Vaccine (2023-2024 Formula):

- 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:

- Preclinical data demonstrating that Moderna COVID-19 Vaccine (2023-2024 Formula) when administered to vaccine naive and vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to the bivalent vaccine (Original and Omicron BA.4/BA.5) against XBB-related sublineages,
- Chemistry, Manufacturing and Control Information related to single dose vial presentation of Moderna COVID-19 Vaccine (2023-2024 Formula) including the manufacturing facilities,
- Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the Moderna COVID-19 Vaccine (Original monovalent) and the Bivalent Vaccine (Original and Omicron BA.1),
- Postmarketing safety surveillance data of the original Moderna COVID-19 Vaccine and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and,
- Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies.

- Although available evidence suggests that the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) continues to provide protection against serious disease from COVID-19 in the U.S., based on the totality of available scientific evidence, it is reasonable to conclude that the Moderna COVID-19 Vaccine (2023-2024 Formula), administered as a single dose to all immunocompetent individuals (unvaccinated or vaccinated) 5 through 11 years of age at least 2 months following any prior original monovalent or 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 XBB-related-sublineages.

- Based on the totality of available scientific evidence, in previously unvaccinated immunocompetent individuals 6 months through 4 years of age, it is reasonable to conclude that the Moderna COVID-19 Vaccine (2023-2024 Formula), administered as two doses may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.

- Based on the totality of available scientific evidence, in immunocompetent individuals 6 months through 4 years of age who have already received one dose of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), it is reasonable to conclude that the Moderna COVID-19 Vaccine (2023-2024 Formula), administered as a single dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.

- Based on the totality of available scientific evidence, in immunocompetent individuals 6 months through 4 years of age who have already received two or more doses of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent, it is reasonable to conclude that the Moderna COVID-19 Vaccine (2023-2024 Formula), administered as a single dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.

- Based on the totality of available scientific evidence, it is reasonable to conclude that administration of age-appropriate dose(s) of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals with certain kinds of immunocompromise 6 months through 11 years of age, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages as noted below:

    - a three-dose series in unvaccinated immunocompromised individuals
    - one or two dose(s) administered as appropriate to complete the three-dose series in immunocompromised individuals previously vaccinated with Moderna COVID-19 Vaccine (Original monovalent) and/or the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
    - a single dose administered at least 2 months after the last previous dose of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated immunocompromised individuals 6 months through 4 years of age, who have received three or more doses
    - a single dose administered at least 2 months following the last previous dose of a COVID-19 vaccine (Original monovalent) or a bivalent COVID-19 vaccine in previously vaccinated immunocompromised individuals 5 through 11 years of age, who have received three or more doses
    - an additional dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in immunocompromised individuals 6 months through 4 years of age at least 2 months following the last dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in at least a three-dose series in which at least 1 dose was with Moderna COVID-19 vaccine (2023-2024 Formula)
    - an additional dose of Moderna COVID-19 Vaccine (2023-2024 Formula) in immunocompromised individuals 5 through 11 years of age at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula) in at least a three-dose series in which at least 1 dose was with a COVID-19 vaccine (2023-2024 Formula)
    - age-appropriate additional doses of Moderna COVID-19 Vaccine (2023-2024 Formula) administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances, with the timing of the additional doses based on the individual's clinical circumstances.

- As summarized in section 6, effectiveness of the Moderna COVID-19 Vaccine (2023-2024 Formula) is supported by 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 (2023-2024 Formula) 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 individuals 6 months through 11 years of age.

- Known and potential benefits of the Moderna COVID-19 Vaccine (2023-2024 Formula) include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to XBB-related sublineages.

- 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: 1) removing authorization for emergency use of the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in the U.S.; and 2) revision of the EUA to provide for use of the Moderna COVID-19 Vaccine (2023-2024 Formula) administered in an appropriate schedule based on age and immune status, as reflected in the Fact Sheets.

10 References

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11 Appendices

Appendix A. Adverse Events of Special Interest

Body System/Classification **Adverse Event of Special Interest**	**Estimated Risk Window (Days)**
Autoimmune diseases	--
Guillain-Barré syndrome[1]	1-42
Acute disseminated encephalomyelitis	1-42
Narcolepsy[1]	1-42[2]
Acute aseptic arthritis	1-42[4]
Diabetes (type 1 and broader)	Any
(Idiopathic) thrombocytopenia[1]	1-42
Heparin-induced thrombocytopenia (HIT)–like event[1]	1-15
Cardiovascular system	--
Acute cardiovascular injury including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia	Any[5]
Myocarditis[1], Pericarditis[1], Myocarditis and pericarditis[1]	1-14 after each dose 1-7 after each dose
Circulatory system	--
Coagulation disorders: thromboembolism, hemorrhage	1-28
Single organ cutaneous vasculitis	1-286
Hepato- gastrointestinal and renal system	--
Acute liver injury	1-42[8]
Acute kidney injury	1-42[8]
Acute pancreatitis	1-42[8]
Rhabdomyolysis	Any
Nerves and central nervous system	--
Generalized convulsion	1-42
Meningoencephalitis	1-42
Transverse myelitis[1]	1-42
Bell's palsy	1-42

Body System/Classification **Adverse Event of Special Interest**	**Estimated Risk Window (Days)**
Respiratory system	--
Acute respiratory distress syndrome	Any
Skin and mucous membrane, bone and joints system	--
Erythema multiforme	1-42[7]
Chilblain-like lesions	1-42[6]
Other system	
Anosmia, ageusia	1-42
Anaphylaxis[1]	1
Multisystem inflammatory syndrome	1-42[3]
Death (any causes)	Any
Subacute thyroiditis	1-42[4]
Sudden death	Any
Gestational diabetes	Any time pregnancy
Pregnancy outcome, maternal	--
Preeclampsia	Any time pregnancy
Maternal death	Any time pregnancy
Fetal growth restriction	Any time pregnancy
Pregnancy outcome, neonates. Define design taking trimester into account	--
Spontaneous abortions	After vaccination
Stillbirth	After vaccination
Preterm birth	At preterm birth
Major congenital anomaliesa	1 year after birth
Microcephaly	At birth
Neonatal death	At birth
Termination of pregnancy for fetal anomaly	At termination
COVID-19 Disease	Any
Any	--
Vaccine-associated enhanced disease (VAED)[1]	Any

Source: Sponsors Clinical Study Protocol C4591021

1. For this AESI clinical validation will occur.
2. Published risk and control intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy/cataplexy.
3. As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1-42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset.
4. Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).
5. Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, coronary artery disease, arrhythmia, acute myocardial infarction).
6. Similar risk and control intervals were applied to all cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, deep venous thrombosis, pulmonary embolus, limb ischemia, hemorrhagic disease, disseminated intravascular coagulation , chilblain-l ke lesions). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.
7. Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).
8. Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other COVID-19 related safety events of interest.

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.

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

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

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

Source: Sponsor's Clinical Overview, mRNA-1273-P203, Section 7.5.5.
Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.
Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.
a. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).
b. Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.
c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).
d. Adler et al 2015.
e. Typically descr bed as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.