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

Application Type	EUA Amendment
Application Number	EUA 27073, Amendments 701-716
Sponsor	ModernaTX, Inc
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Review Completion Date	August 22, 2024
Established Name/Names used during development	Moderna COVID-19 Vaccine (2024-2025 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 7, 2024, SARS-CoV-2 has caused over 775 million cases of coronavirus disease 2019 (COVID-19), including 7 million deaths worldwide, and immense societal, economic, and healthcare system disruptions. COVID-19 vaccination remains a core prevention strategy in the United States (U.S.), as staying up to date on COVID-19 vaccines significantly lowers the risk of COVID-19-related morbidity and mortality (CDC 2024). 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 (Watson et al. 2022).

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). As SARS-CoV-2 evolved, the Moderna COVID-19 vaccine formula has been periodically updated. For more details on the composition and authorizations of Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula) refer to Moderna COVID-19 Vaccine Decision Memos and Regulatory Documents. Although the Moderna COVID-19 Vaccine is now licensed for individuals 12 years of age and older under the tradename Spikevax, the vaccine remains under Emergency Use Authorization (EUA) for those 6 months through 11 years of age.

On September 11, 2023, FDA authorized use of Moderna COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months through 11 years of age according to an age-appropriate dosing schedule, including additional age-appropriate doses for persons with certain kinds of immunocompromise. FDA also approved the use of Spikevax (COVID-19 Vaccine, mRNA) (2023-2024 Formula) for use as a single dose in individuals 12 years of age and older. For details, please refer to Spikevax.

Since the introduction of COVID-19 vaccines (2023-2024 Formula) in fall 2023, SARS-CoV-2 has continued to evolve into distinct new Omicron Variant of Concern (VOC) parent lineages and descendant variants by acquiring additional mutations. Although real-world effectiveness studies suggest that currently approved/authorized COVID-19 vaccines (2023-2024 Formula) continue to provide protection against currently circulating Omicron JN.1-lineage descendant variants, in prior years an inverse relationship between the time since vaccination and vaccine effectiveness has been observed, such that COVID-19 vaccine effectiveness against new SARS-CoV-2 variants appears to wane over time (Link-Gelles et al. 2023) and that closer matching of COVID-19 vaccine formulas to circulating new parent lineage descendant variants is associated with improved neutralizing antibody titers (Jiang et al. 2023). Consistent with this observation, a decrease in effectiveness of COVID-19 vaccines (2023-2024 Formula) against COVID-19 caused by JN.1-lineage descendant variants has been reported (Kirsebom et al. 2024; Shrestha et al. 2024).

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened on June 5, 2024 in open session to discuss and make recommendations on the selection of an updated formula for COVID-19 vaccines. VRBPAC endorsed a monovalent JN.1-lineage COVID-19 vaccine (2024-2025 Formula) and was in overall agreement that JN.1 should be the selected lineage descendent variant. Although the evidence presented to VRBPAC, including nonclinical data generated from “at-risk” candidate vaccines, did not definitively point to an advantage of selecting a specific variant (e.g., JN.1 or KP.2) for inclusion in the 2024-2025 Formula, based on the totality of evidence available, FDA initially advised manufacturers of U.S.-licensed and -authorized COVID-19 vaccines that COVID-19 vaccines (2024-2025 Formula) for use in the U.S. beginning in fall 2024 should be monovalent JN.1

vaccines. FDA continued to monitor emerging data and based on FDA's assessment of the available evidence (refer to section 3.2), FDA determined that KP.2, if feasible, was the preferred JN.1-lineage descendant variant for COVID-19 vaccines (2024-2025 Formula). FDA communicated this update to manufacturers of U.S.-licensed and -authorized COVID-19 vaccines on June 13, 2024. Based on the updated recommendation, ModernaTX Inc., on June 20, 2024, requested authorization of their COVID-19 vaccine to include a monovalent KP.2-based 2024-2025 Formula.

The clinical effectiveness and safety data accrued with the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Moderna's bivalent COVID-19 Vaccine (Original and Omicron BA.1) are relevant to Moderna COVID-19 Vaccine, (2024-2025 Formula), because these vaccines are manufactured using the same process. The effectiveness and safety of Moderna COVID-19 Vaccine (2024-2025 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) reviewed in section 6.1.

Postmarketing effectiveness and safety data for Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (Original monovalent) were considered relevant to the effectiveness and safety evaluation and benefit-risk assessment of Moderna COVID-19 Vaccine (2024-2025 Formula), because Moderna COVID-19 Vaccine (2024-2025 Formula) is manufactured using the same process as Moderna COVID-19 Vaccine (2023-2024 Formula), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (Original monovalent). Review of postmarketing safety data indicate a similar safety profile of the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula).

Cumulative global data submitted by the Sponsor indicated distribution of (b) (4) doses of all Moderna COVID-19 vaccine formulations in all ages as of June 17, 2024, including (b) (4) doses of Moderna COVID-19 Vaccine (2023-2024 Formula). In the Sponsor global safety database, cumulatively through June 17, 2024, the Sponsor received 3,290 cases of adverse events specifically in individuals 6 months through 11 years who received any Moderna vaccine targeting SARS-CoV-2 (see section 6.2 for further details).

Cumulative U.S. data submitted by the Sponsor indicated distribution of (b) (4) doses of all Moderna COVID-19 vaccine formulations in all ages including (b) (4) doses of Moderna COVID-19 Vaccine (2023-2024 Formula). The most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were: incorrect dose administered, expired product administered, product administered to patient of inappropriate age, pyrexia, wrong product administered, underdose, product storage error, incorrect product formulation administered, vomiting, and inappropriate schedule of product administration. In view of the findings of a small number of febrile seizures following administration of Moderna COVID-19 Vaccine (Hu et al. 2024; Forshee et al. 2024) as well as VAERS reports of febrile seizures following administration of Moderna COVID-19 Vaccine, a labeling change was made to the *Postmarketing Experience* section of the Fact Sheet for Health Care Providers Administering Vaccines and the *What are the Risks of Moderna COVID-19 Vaccine* section of Fact Sheet for Recipient and Caregivers to include *Febrile seizure* on the list of adverse reactions identified during postmarketing use.

The Sponsor is conducting (or has completed) 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).

As noted above, safety and effectiveness data accrued with Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula) are relevant to Moderna COVID-19 Vaccine (2024-2025 Formula), because all these vaccines are manufactured using the same process. In addition, the nonclinical data reviewed indicate that Moderna COVID-19 Vaccine (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Moderna COVID-19 Vaccine (2023-2024 Formula) against JN.1-lineage descendant variants. 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 (2024-2025 Formula) compared with Moderna COVID-19 Vaccine (2023-2024 Formula), will likely increase immune responses and protection against COVID-19 caused by SARS- CoV-2 variants, including currently predominant JN.1-lineage descendant variants.

During the review of this EUA amendment request, FDA also considered a minor change to the dosing schedule under the EUA for individuals with certain kinds of immunocompromise. Under the EUA, this change would authorize the use of one or two doses, as applicable, of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) to complete the three-dose vaccination series in individuals with certain kinds of immunocompromise turning from 11 to 12 years of age during the three-dose vaccination series, on or after the date the individual turns 12 years of age. Evidence discussed in section 6, along with the evidence supporting licensure of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula), supports this use of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) under EUA.

Taken together, the Review Team recommends: 1) discontinuation of use of the Moderna COVID- 19 Vaccine (2023-2024 Formula) for use in the U.S.; 2) use of age-appropriate doses and dosing schedules of the Moderna COVID-19 Vaccine (2024-2025 Formula) in individuals 6 months through 11 years of age, based on immune status and previous vaccination status; and 3) use of appropriate dosing of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) in certain immunocompromised individuals turning 11 to 12 years of age during the three-dose vaccination series.

2 Background

2.1 SARS-CoV-2 Virus and COVID-19

SARS-CoV-2 emerged as a zoonotic coronavirus in late 2019 in patients with pneumonia of unknown cause. SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), infects a broad range of hosts and presents in humans with variable respiratory and systemic manifestations. As of August 6, 2024, SARS-CoV-2 infection has resulted in over 775 million cases of COVID-19 and an estimated 7 million deaths worldwide (World Health Organization 2021a). 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 (CDC 2023d), 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 (CDC 2023a; National Academies of Sciences 2024a). Symptoms associated with SARS-CoV-2 infection in most children are similar to those in adults but are generally milder, with fever and cough most commonly reported (Liguoro et al. 2020; Irfan et al. 2021). However, since the October 2023 surge in cases due to Omicron XBB- and JN.1-lineage descendant

variants, rates of COVID-19-associated hospitalizations are as high in infants younger than 6 months who are not vaccine eligible as in individuals 65 through 74 years of age (CDC 2023c).

In the U.S., more than 6.9 million COVID-19-associated hospitalizations and 1.2 million deaths have been reported to the Centers for Disease Control and Prevention (CDC) (CDC 2023b). Individuals 65 years of age and older accounted for approximately 14% of cases and 76% of death. During October 2023 through May 2024, individuals 65 years of age and older accounted for 67% of COVID-19 hospitalizations; in contrast, individuals 17 years of age and younger accounted for 4% of COVID-19 hospitalizations, with individuals less than 6 months of age accounting for most of those hospitalizations (Havers FP, 2024). 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. The XBB-lineage descendant XBB.1.5 variant spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world by April 2023. Monovalent XBB.1.5-based COVID-19 vaccines (2023-2024 Formula) were deployed in the U.S. starting in September 2023.

The JN.1 variant, a descendant of the Omicron BA.2.86 lineage containing a new L455S mutation, was first detected in August 2023 and subsequently became the dominant variant by January 2024. The JN.1 variant remained dominant during the remainder of winter and early spring 2024. However, in February 2024, the JN.1-lineage descendant KP.2 variant containing two new mutations, i.e., F456L and R356T, that appear to confer an advantage to the virus either in terms of fitness or escape from immunity, became noticeable.

SARS-CoV-2 evolution continues to be complex and remains unpredictable. There is no indication that SARS-CoV-2 evolution is slowing, though immunity, acquired by infection, vaccination, or both, appears to mitigate severe clinical outcomes, particularly in younger populations. Intrinsic viral factors, including mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. At the same time, host immune responses and other factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in immunocompromised hosts or potentially by waning of immunity in immunocompetent hosts. Thus far, the impressive plasticity, especially in Spike, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the critical importance of ongoing global surveillance.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

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

2.2.1 Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) and Moderna COVID-19 Vaccine (2023-2024 Formula)

Spikevax (COVID-19 Vaccine, mRNA) (COVID-19 Vaccine, mRNA) (2024-2025 Formula) manufactured by Moderna is approved for active immunization to prevent coronavirus disease 2019

(COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (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 the JN.1-lineage descendant KP.2 variant, encapsulated in lipid particles. Moderna COVID-19 Vaccine (2023-2024 Formula), a formulation of the vaccine manufactured using the same process as Spikevax, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 years of age and older, two-dose regimen in those individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, and a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with Moderna COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age may be administered additional age-appropriate doses as described in the authorized dosing schedule. For additional information on dosing and schedule, please refer to the Moderna COVID-19 Vaccine (2023-2024 Formula) Fact Sheets. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine (2023-2024 Formula) are detailed in the decision memoranda available on the FDA Website.

2.2.2 Comirnaty (2024-2025 Formula) and Pfizer-BioNTech COVID-19 Vaccine, (2023-2024 Formula)

Comirnaty (COVID-19 Vaccine, mRNA) (2024-2025 Formula) manufactured by Pfizer for BioNTech, is approved for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Comirnaty contains a mRNA encoding the viral Spike (S) glycoprotein of the JN.1-lineage descendant KP.2 variant that is formulated in lipid particles. Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), a formulation of the vaccine manufactured using the same process as Comirnaty, is currently authorized under EUA for administration of a single-dose regimen to individuals 5 years of age and older, three-dose regimen in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two-dose regimen in individuals 6 months through 4 years of age if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single-dose regimen to individuals 6 months through 4 years of age previously vaccinated with two to four doses of Pfizer BioNTech COVID-19 Vaccine. Individuals with certain kinds of immunocompromise 6 months through 11 years of age may be administered additional age-appropriate doses as described in the authorized dosing schedule. For additional information on dosing and schedule, please refer to the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Fact Sheets. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) are detailed in the decision memoranda available on the FDA Website.

2.2.3 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)

Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), which contains recombinant S protein of the Omicron XBB-lineage descendant XBB.1.5 variant and Matrix-M adjuvant, is authorized for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is currently authorized under EUA for administration of a single-dose regimen at least 2 months after receipt of the last previous dose of COVID-19 vaccine to individuals 12 years of age and older previously vaccinated with any COVID-19 vaccine. In individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is currently authorized under EUA for administration as a two-dose regimen. Individuals with certain kinds of immunocompromise 12 years of age and older may be administered additional age-appropriate doses as described in the

authorized dosing schedule. For additional information on dosing and schedule, please refer to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) 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 emergency use by healthcare providers for the treatment of mild-to-moderate COVID-19 in 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 were authorized under EUA but are not currently authorized due to the high frequency of resistant circulating SARS-CoV-2 variants (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 7, 2023).

Pemivibart (Pemgarda), a SARS-CoV-2 spike protein-directed IgG1mAb, has been authorized under EUA for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents (12 years of age and older weighing at least 40 kg): i) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and: ii) who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination. Pemgarda is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

Immune modulators:

Anakinra (Kineret) 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).

Vilobelimab (Gohibic) 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 (Olumiant) 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 (Actemra) 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 COVID-19 vaccines (2023-2024 Formula) and Need for Strain Update

Several observational studies (DeCuir et al. 2024; Joshi et al. 2024; Link-Gelles et al. 2024) have been conducted to evaluate the effectiveness of COVID-19 vaccines (2023-2024 Formula) introduced after emergence and global dominance of XBB-lineage descendant variants. These studies indicate that

updating COVID-19 vaccines to an XBB.1.5-based formula was associated with positive health outcomes, including a reduction in hospitalization and urgent care utilization.

Since the introduction of COVID-19 vaccines (2023-2024 Formula) in fall 2023, SARS-CoV-2 has continued evolving into distinct Omicron parent lineages and descendant variants by acquiring additional mutations. Although real-world effectiveness studies suggest that approved/authorized COVID-19 vaccines (2023-2024 Formula) continue to provide protection against more currently circulating XBB- and JN.1-lineage descendant variants, in prior years there appears to have been an inverse relationship between the time since vaccination and vaccine effectiveness, such that COVID-19 vaccine effectiveness against new SARS-CoV-2 variants appears to wane over time (Link-Gelles et al. 2023) and that better matching of the vaccine to circulating strains is associated with improved neutralizing antibody titers (Jiang et al. 2023). Consistent with this observation, a decrease in effectiveness of COVID-19 vaccines (2023-2024 Formula) against COVID-19 caused by JN.1-lineage descendant variants has been reported (Kirsebom et al. 2024; Shrestha et al. 2024).

Available data suggest that updating the current formula of COVID-19 vaccines to more closely match currently circulating JN.1-lineage descendant variants is warranted for the anticipated 2024-2025 respiratory virus season in the U.S.

3.2 Recommendations for COVID-19 Vaccines 2024-2025 Formula for Use 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 an updated formula for 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 VRBPAC in June of each year regarding formula selection for COVID-19 vaccines for fall vaccination.

As noted above (section 2.1), the JN.1 variant that became dominant in North America and the rest of the world in late 2023 and early 2024 was the dominant variant through much of spring 2024, having replaced the previous XBB-lineage descendent variants that had dominated earlier in 2023. The XBB-lineage arose from a recombinant of two BA.2 derived viruses, BA.2.10.1 and BA.2.75, with substantial Spike amino acid changes compared with the original BA.2 that included multiple amino acid mutations in the Spike receptor binding domain (RBD). The JN.1 variant is a descendant of the BA.2.86-lineage with a new L455S RBD mutation. Overall, BA.2.86 and the more recent related JN.1-lineage descendant variants contain over 30 Spike protein mutations in comparison with XBB-lineage descendant variants, suggesting the potential for evasion of immunity elicited by prior infection and/or vaccination. Although both XBB- and JN.1-lineages descended from earlier BA.2-lineage descendent variants, the lineages evolved separately and are antigenically distinct.

The JN.1 variant continued to evolve during spring 2024, giving rise to a group of JN.1-lineage descendant variants, many of which, such as KP.2, contain concerning new mutations in Spike RBD, most notably the so-called FLiRT mutations at F456L and R356T. While the landscape of JN.1-lineage descendant variants is quite diverse, currently the original JN.1 variant has almost disappeared. JN.1-lineage descendant variants containing F456L along with R346T and more recently T572I (e.g., KP.3) are found to be highly prevalent worldwide. Preliminary data from several laboratories indicate that these RBD mutations result in a further decrease in neutralizing antibody titers that were elicited by prior vaccination and/or infection with previously circulating strains. In summary, the lower neutralizing antibody titers elicited by vaccination, infection, or hybrid immunity against current JN.1-lineage descendant subvariants, including KP.2, and other FLIRT variants, suggest that individuals previously

infected with an XBB-lineage descendant variants and/or immunized with an XBB.1.5-based COVID-19 vaccine may be susceptible to COVID-19 caused by currently circulating JN.1-lineage descendant variants, and potentially other future COVID-19 variants.

On June 5, 2024, VRBPAC convened in open session to discuss and make recommendations on the selection of an updated formula for COVID-19 vaccines. In preparation for a possible composition update for a 2024-2025 Formula, manufacturers of currently authorized or approved mRNA COVID-19 vaccines had evaluated "at-risk" two candidate vaccine prototypes (i.e., JN.1 and KP.2) and presented nonclinical data to VRBPAC. VRBPAC considered several factors in their recommendation, including timelines for updated vaccine availability. In general, manufacturers indicated a shorter timeline for mRNA vaccine formula changes compared with protein subunit vaccines.

VRBPAC endorsed a monovalent JN.1-lineage vaccine composition for the 2024-2025 Formula of COVID-19 vaccines in the U.S. and was in overall agreement with JN.1 as a selected JN.1-lineage variant. The evidence presented to VRBPAC, including nonclinical data generated from "at-risk" candidate vaccines, did not definitively suggest selection of KP.2 over JN.1 composition for inclusion in 2024-2025 Formula. Based on the totality of evidence available, FDA therefore initially advised manufacturers of U.S.-licensed and -authorized COVID-19 vaccines that COVID-19 vaccines (2024-2025 Formula) for use in the U.S. beginning in fall 2024 should be monovalent JN.1 vaccines.

FDA continued to monitor and reassess evolving and emerging data including U.S. and regional variant proportions (e.g., CDC Now Cast Weighted Estimates), and observations on reduced cross-reactivity of sera from JN.1-infected individuals against JN.1-lineage descendent KP.2, and other variants of the JN.1-lineage (Li et al. 2024). Based on additional available evidence, FDA determined that KP.2, if feasible, was a preferred JN.1-lineage descendant variant for COVID-19 vaccines (2024-2025 Formula). FDA communicated this updated advice to manufacturers of U.S.-licensed and -authorized COVID-19 vaccines on June 13, 2024.

4 Regulatory Considerations for EUA of a Monovalent COVID-19 Vaccine

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.

5 EUA Amendment Request to Include the 2024-2025 Formula for Moderna COVID-19 Vaccine

5.1 Summary of the EUA Request

Following VRBPAC discussion on June 5, 2024, and FDA's updated advice to manufacturers on June 13, 2024 (section 3.2), ModernaTX Inc., requested, on June 20, 2023, authorization of their COVID-19 vaccine to include a monovalent KP.2-based 2024-2025 Formula with the same dose and administration schedule authorized for Moderna COVID-19 Vaccine (2023-2024 Formula). Moderna's request was supported by the following information:

- Nonclinical data
- Chemistry, Manufacturing and Control (CMC) information for Moderna COVID-19 Vaccine (2024-2025 Formula)
- A Pharmacovigilance plan

During its consideration of Moderna's request, FDA also considered a minor change to the dosing schedule under the EUA for individuals with certain kinds of immunocompromise. This change would authorize the use of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) to complete the three-dose vaccination series for individuals turning from 11 to 12 years of age during the series on or after the date the individual turns 12 years of age. Specifically, if the individual turning 12 years of age receives two doses of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) to complete the vaccination series or receives a dose of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) less than 2 months after receipt of the last previous dose of COVID-19 vaccine to complete the vaccination series, then those uses of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) would be authorized under EUA. This change was considered to simplify use of age-appropriate doses and foster clearer communication to vaccination providers, with the intent to reduce vaccine administration errors and potentially improve vaccine uptake.

5.2 FDA's Approach for Selection of Antigens to be Included in 2024-2025 Formula for COVID-19 Vaccines

In previous discussions with VRBPAC, FDA described the proposed evidentiary basis that would be used to determine the need for updating the antigen composition of COVID-19 vaccines. The relevant data reviewed would ideally include multiple types and sources of data.

The International Coalition of Medicines Regulatory Authorities (ICMRA) is an informal group of international regulatory authorities that promotes collaboration and communication to address common challenges. At an ICMRA workshop entitled "Global Perspectives on COVID-19 Vaccines Strain Update" held February 26-27, 2024, FDA and other regulators met to discuss global regulatory alignment to adapt COVID-19 vaccines to emerging SARS-CoV-2 variants and to discuss the preferred strain composition for future vaccine updates. The conclusions of the meeting included: that use of prior knowledge on a specific product could be used for the approval of strain changes for currently authorized or approved COVID-19 vaccines; Spike antigen change procedures should take into consideration all available information and data from studies; at the present time an updated vaccine composition for currently authorized or approved COVID-19 vaccines can be based on quality and non-clinical data; and that post-authorization commitments may be needed to gather data on vaccine effectiveness against severe outcomes as well as symptomatic disease. Immunogenicity data from clinical trials conducted using updated vaccines when they become available are important to support future antigen change decisions. Additionally, it was noted that at the present time there are no apparent differences in SARS-CoV-2 circulation and transmission in the Northern and Southern Hemispheres.

WHO established the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) to review and assess the public health implications of emerging SARS-CoV-2 variants of concern (VOCs) on the performance of COVID-19 vaccines and to provide recommendations to WHO on COVID-19 vaccine strain composition. On April 26, 2024, TAG-CO-VAC issued a statement on the antigen composition of COVID-19 vaccines, summarizing the data reviewed by the group on the antigenicity and cross-protection following infection and/or vaccination in the context of currently circulating XBB viruses.

In preparation for the June 2024 VRBPAC discussion, FDA reviewed various types of data as summarized in FDA Briefing Document for June 5, 2024 VRBPAC, engaged with key partners generating such data, including vaccine manufacturers and other U.S. government agencies, and reviewed discussions and recommendations put forth by other regulatory and public health agencies, as noted above.

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).

Currently, circumstances exist that make it appropriate to revise the EUA with respect to the Moderna COVID-19 Vaccine (2023-2024 Formula) to protect the public health. As outlined in section 1, the Moderna COVID-19 Vaccine (2023-2024 Formula) is authorized for use in individuals 6 months through 11 years of age. Authorization of the Moderna COVID-19 Vaccine (2024-2025 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 variants of SARS-CoV-2, resulting in a more favorable anticipated benefit-risk assessment for the Moderna COVID-19 Vaccine (2024-2025 Formula). FDA has also approved a supplemental biologics license application for Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula), which contains mRNA encoding the viral spike (S) glycoprotein of KP.2, 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 the 2023-2024 Formula for use in the U.S. ensures that vaccination programs will continue to use a single vaccine strain composition for Moderna's COVID-19 vaccines, which should continue to help minimize vaccine

administration errors that would result from availability of multiple different vaccine strain compositions and also potentially encourage vaccine uptake. Consequently, revising the EUA to remove authorization of the Moderna COVID-19 Vaccine (2023-2024 Formula) 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 (2023-2024 Formula) may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Moderna COVID-19 Vaccine (2023-2024 Formula) 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 (2023-2024 Formula) is currently authorized. Therefore, it is appropriate to continue to authorize the Moderna COVID-19 Vaccine (2023-2024 Formula) for export.

Accordingly, authorization of the Moderna COVID-19 Vaccine (2024-2025 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 (2023-2024 Formula) 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 (2023-2024 Formula) 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.

The current EUA also authorizes the export of previously manufactured Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), subject to comparable conditions. However, the available information indicates that lots of these vaccines are no longer within their expiry dates and/or are no longer being distributed by the manufacturer. Based on the available information, circumstances exist that make it appropriate to revise the EUA to no longer provide for the export of the Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and doing so is appropriate to protect the public health or safety.

6 FDA Review of Clinical Effectiveness and Safety Data

6.1 Overview of Clinical Studies

The clinical effectiveness and safety data accrued with Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) (both no longer authorized for use in the U.S.), and Moderna's bivalent COVID-19 Vaccine (Original and Omicron BA.1) (not approved or authorized in U.S.) are relevant to Moderna COVID-19 Vaccine (2024-2025 Formula), because all these vaccines are manufactured using the same process. For a high-level summary of previously reviewed data that support the clinical effectiveness and safety of Moderna COVID-19 Vaccine (2024-2025 Formula) for individuals 6 months through 11 years of age, please refer to the section 6 of the EUA Decision Memorandum dated September 11, 2023.

6.1.1 Immunocompromised Individuals

The safety and effectiveness of a three-dose series of Moderna COVID-19 Vaccine (2024-2025 Formula) in individuals 6 months through 11 years of age with certain kinds of immunocompromise and safety and effectiveness of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) for use in individuals with certain kinds of immunocompromise turning from 11 years to 12 years of age during the three-dose series to complete the series on or after the date they turn 12 years of age is based on safety and effectiveness of a two-dose primary series in children 6 months through 17 years of age and third primary series dose in adults with certain kinds of immunocompromise (For detailed review of the evidence, please refer to FDA Review Memorandum Dated August 12, 2021 and June 17, 2022).

The safety and effectiveness of additional doses of Moderna COVID-19 Vaccine (2024-2025 Formula) for individuals 6 months through 11 years of age with certain kinds of immunocompromise is based on the same evidence for use of additional doses of Moderna COVID-19 Vaccine (2023-2024 Formula) for such individuals, as described in section 6 of the EUA Decision Memorandum dated September 11, 2023.

6.1.2 Conclusion

The clinical effectiveness and safety data accrued with the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Moderna's bivalent COVID-19 Vaccine (Original and Omicron BA.1) are relevant to Moderna COVID-19 Vaccine, (2024-2025 Formula), because these vaccines are manufactured using the same process. The effectiveness and safety of Moderna COVID-19 Vaccine (2024-2025 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) and additional safety data reviewed in section 6.2 below.

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 (2024-2025 Formula) may be effective in individuals 6 months through 11 years of age. In addition, the nonclinical data reviewed indicate that Moderna Vaccine (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Moderna COVID-19 Vaccine (2023-2024 Formula) against JN.1-related descendant variants. It is further reasonable to expect that Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) may be effective in individuals with certain kinds of immunocompromise turning from 11 years to 12 years of age during the three-dose series when used to complete the series on or after the date they turn 12 years of age.

Consequently, to address the urgent public health need for COVID-19 vaccines more closely matched to circulating SARS-CoV-2 variants, FDA considers it appropriate to authorize the emergency use of the Moderna COVID-19 Vaccine (2024-2025 Formula) based on relevant clinical effectiveness and safety evidence from previously authorized and currently authorized or approved Moderna COVID-19 vaccines manufactured using the same process, in addition to supportive nonclinical animal data for Moderna COVID-19 Vaccine (2024-2025 Formula) and to authorize certain uses of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) in individuals with certain kinds of immunocompromise turning from 11 years to 12 years of age during the three-dose series.

6.2 Additional Safety Data

Given that Moderna COVID-19 Vaccine (2024-2025 Formula) is manufactured using the same process as Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula), cumulative postmarketing safety data for Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent 2024 Formula) were considered relevant to the comprehensive safety evaluation of the Moderna COVID-19 Vaccine (2024-2025 Formula).

6.2.1 Postmarketing Safety

Review of postmarketing safety data indicate a similar safety profile of the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula). The sponsor submitted data that indicate a cumulative global distribution of (b) (4) doses of all formulations in all ages as of June 17, 2024, including (b) (4) doses of Moderna COVID-19 Vaccine (2023-2024 Formula). In the global safety database, cumulatively through June 17, 2024, the Sponsor received 3,290 cases of adverse events (AEs) in individuals 6 months through 11 years who received any Moderna vaccine targeting SARS-CoV-2. Of these, 3,046 (92.6%) AEs were non-serious, 244 (7.4%) AEs were serious, and six (0.2%) AEs reported a fatal outcome. Of the 3,290 cumulative AE reports, 411 AEs involved the 2023-2024 Formula. Of these 411 AEs, 10 (2.4%) were serious. No fatalities were reported. Postmarketing safety data relevant to use of Spikevax (2024-2025 Formula) in individuals who are 12 years of age and older were also reviewed in support of this EUA. For detailed review of these data, please refer to the pharmacovigilance memorandum supporting the approval of STN 125752/220.

Cumulative U.S. data submitted by the sponsor indicated distribution of (b) (4) doses of all Moderna COVID-19 vaccine formulations in all ages including (b) (4) doses of Moderna COVID-19 Vaccine (2023-2024 Formula). The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following all doses of Moderna COVID-19 vaccines (Original monovalent, Bivalent, and 2023-2024 Formula) among children 6 months to less than 12 years of age. As of June 17, 2024, there were 4,693 events, of which 278 (5.9%) were reported as serious and eight (0.2%) involved a fatality. All death reports were individually reviewed. There were no reports of deaths that were attributed to Moderna COVID-19 vaccines based on FDA medical review of the cases. The most frequently reported preferred terms (PTs) were: incorrect dose administered, expired product administered, product administered to patient of inappropriate age, pyrexia, wrong product administered, underdose, product storage error, incorrect product formulation administered, vomiting, and inappropriate schedule of product administration.

Febrile seizure: Two recent studies evaluated febrile seizures among children 2 through 5 years of age. A study entitled “Safety of Ancestral Monovalent BNT162b2, mRNA-1273, and NVX-CoV2373 COVID-19 Vaccines in US Children Aged 6 Months to 17 Years” detected a statistical signal for seizures in 2 through 5 years of age. A second study (medRxiv preprint) entitled “Evaluation of Febrile Seizure Risk Following Ancestral Monovalent COVID-19 mRNA Vaccination Among U.S. Children Aged 2-5 Years” performed a self-controlled case series analysis that included participants aged 2 through 5 years from three commercial insurance databases, and found that the incidence rate ratio (IRR) of febrile seizures was significantly elevated (IRR: 2.52, 95% CI: 1.35 to 4.69,) in the 0-1 days following mRNA-1273 administration. Absolute risk was small. A query of VAERS data on June 6, 2024, for “febrile seizure” for Moderna COVID-19 vaccines (Original monovalent or 2023-2024 Formula), in individuals <18 years of age, identified 37 reports (including 19 serious reports and 18 non-serious reports). In view of the findings on febrile seizures following administration of Moderna COVID-19 Vaccine described above as well as VAERS reports of febrile seizures following administration of Moderna COVID-19 vaccines, a

labeling change was made to the *Postmarketing Experience* section of the Fact Sheet for Health Care Providers Administering Vaccines and the *What are the Risks of Moderna COVID-19 Vaccine* section of Fact Sheet for Recipient and Caregivers to include *Febrile seizure* on the list of adverse reactions identified during postmarketing use.

For important risks identified in the pharmacovigilance plan for Moderna COVID-19 vaccines, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting (or has completed) 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).

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 Moderna COVID-19 Vaccine (2024-2025 Formula) (code number mRNA-1273.712) for use in individuals 6 months through 11 years of age is supplied in a single-dose Pre-filled Syringe (PFS) intended to deliver 0.25 mL of 0.10 mg/mL mRNA-1273.712 Drug Product. Each 0.25 mL dose contains the following ingredients: 0.025 mg of mRNA encoding Spike glycoprotein (S) of SARS-CoV-2 Omicron JN.1-lineage KP.2 variant (mRNA code CX-046684), 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. Moderna COVID-19 Vaccine is provided as a sterile white to off-white injectable suspension for intramuscular use.

The manufacturing process for the Drug Substance (DS) consists of (b) (4) The mRNA-1273.712 Drug Product (DP) is manufactured by adjusting the (b) (4) filling of final containers, and labeling/packaging. The DS manufacturing and controls for KP.2-containing vaccine will be the same as used for the licensed Spikevax prototype and other variant vaccines, with the only exception being (b) (4) The DS manufacturing processes and controls were reviewed under the original EUA request and were adequately characterized and qualified.

The major changes in the DP manufacturing consist of replacing the multiple-dose (0.5 mL) (b) (4) vial presentation with the single-dose (0.25 mL) PFS (referred to as pediatric PFS), and the addition of new manufacturing and testing facilities. To support the EUA amendment request, process-performance qualification (PPQ) data and in-process, release, and characterization results were provided for three pediatric PFS DP lots manufactured at Rovi Pharma Industrial Services, S.A. Julián Camarillo (Madrid, Spain). The DP manufacturing process and controls were adequately characterized and qualified. Once authorized, Moderna will be required under the conditions of authorization to 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 in all QC laboratories involved in analytical testing of pediatric PFS DP lots, including Rovi Pharma Industrial Services, S.A. Julián Camarillo (Madrid, Spain), Rovi Pharma Industrial Services, S.A. Alcala de Henares (Madrid, Spain), Moderna Biotech Spain (Madrid, Spain), (b) (4) and (b) (4) The validation results demonstrated acceptable precision, accuracy, sensitivity, specificity, and reproducibility of the analytical assays, indicating that they are suitable for the quality control of DS and DP.

A shelf life of 10 months from the date of manufacture (DOM) is proposed for the 0.10 mg/mL mRNA-1273.712 DP in 0.25 mL PFS stored at the recommended long-term storage condition of -25°C to -15°C (-20°C), which may include up to 60 days of storage at 2 – 8°C (5°C) and 12 hours at room temperature (25°C) to support administration of the vaccine at the point of care site. The DOM is defined as the start date of packaging and labeling operations. The totality of data available for real-time and sequential stability and the results of statistical analysis for the shelf-life modelling support the proposed 10-month shelf life. All stability studies conducted for mRNA-1273.712 DP are ongoing and will continue to be monitored. Stability data will be submitted to the EUA as they become available.

7.2 Facilities

Moderna COVID-19 Vaccine (2024-2025 Formula) in PFS, for use in individuals 6 months through 11 years of age, is manufactured at existing facilities previously used for manufacturing Moderna COVID-19 Vaccine (2023-2024 Formula), with the exception that the Moderna COVID-19 Vaccine (2024-2025 Formula) drug product (DP) is filled on the (b) (4) line at Rovi Pharma Industrial Services, S.A., Julian Camarillo located in Madrid Spain (referred to as “Rovi JC”). Additionally, select Moderna COVID-19 Vaccine (2024-2025 Formula) DP release testing is performed at Moderna Biotech Spain S.L. in Madrid, Spain (referred to as “Moderna Biotech Spain”). The review of the supporting information for the Rovi JC facility and manufacturing of Moderna COVID-19 Vaccine (2024-2025 Formula) is documented under STN 125752/74 and EUA 27073/703. The review of the supporting information for the Moderna Biotech Spain facility is documented under STN 125752/201. No other changes were made to facilities, equipment, and quality controls for manufacturing of Moderna COVID-19 Vaccine (2024-2025 Formula). FDA finds that the facilities for the manufacture of the Moderna COVID-19 Vaccine (2024-2025 Formula) for use in individuals 6 months through 11 years of age are adequate to support use of the vaccine under an EUA.

7.3 Nonclinical Studies

Two nonclinical studies were completed in mice to evaluate immunogenicity of Moderna COVID-19 Vaccine (2024-2025 Formula) given as a two-dose primary series or as a booster dose following a primary series vaccination with Moderna COVID-19 Vaccine (Original monovalent). The submitted results demonstrated that Moderna COVID-19 Vaccine (2024-2025 Formula) vaccine elicited strong binding and neutralizing antibody responses against KP.2 variant and other JN.1-lineage descendant variants, JN.1, KP.3, and LA.2, after primary and booster vaccinations compared with Moderna COVID-19 Vaccine (2023-2024 Formula). These data are therefore considered supportive for the formula change to Omicron JN.1-lineage KP.2 variant for the Moderna COVID-19 Vaccine (2024-2025 Formula).

7.4 Pharmacovigilance Activities

7.4.1 Sponsor Pharmacovigilance Activities

In addition to adverse event reporting, Moderna is conducting (or has completed) safety-related post-authorization/postmarketing studies for Moderna COVID-19 Original monovalent, Bivalent (Original and Omicron BA.4/BA.5), and 2023-2024 Formula vaccines, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. (Of note, the post-authorization/postmarketing safety studies for Moderna COVID-19 Original monovalent, Bivalent, and 2023-2024 Formula vaccines are either ongoing or completed.) Moderna has a pharmacovigilance plan (PVP) (version 8.5) to monitor postmarketing safety for the Moderna COVID-19 Vaccine (2024-2025 Formula). The PVP 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

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Moderna COVID-19 Vaccine (2024-2025 Formula) including:

- Mandatory reporting by the Sponsor under the EUA for the following events reported 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; actions taken since the last report because of adverse experiences; and cumulative and interval doses distributed; and periodic safety reports are currently being submitted quarterly, and
- Post-authorization observational study to evaluate the association between Moderna COVID-19 Vaccine (2024-2025 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.

    - **Study mRNA-1273-P951.** Postmarketing safety of Moderna vaccines targeting SARS-CoV-2 following the 2024-2025 strain change in the United States.

        Objectives:

        1) Describing the uptake of updated Moderna vaccines targeting SARS CoV-2, characterizing vaccine recipients
        2) Estimating incidence of myocarditis and pericarditis and assessing risk after vaccination

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

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 products under EUA.

8 Benefit-Risk Assessment in the Context of the Proposed EUA for Moderna COVID-19 Vaccine (2024-2025 Formula) in Individuals 6 Months of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

Sections 1 and 2 of this memorandum detail COVID-19 disease epidemiology, SARS-CoV-2 evolution and the available therapeutics/prophylactics that are authorized or approved for COVID-19. These interventions are generally most effective in disease of mild to moderate severity. Although anti-viral-specific treatments exist for those infected with SARS-CoV-2, they are generally not effective for individuals with severe disease and immunomodulators are recommended for treatment with severe disease (section 2). Additionally, such treatments may not prevent complications from COVID-19, including long COVID (National Academies of Sciences 2024b).

COVID-19 vaccination remains a core prevention strategy in the U.S., as staying up to date on COVID-19 vaccines significantly lowers the risk of COVID-19-related morbidity and mortality (CDC 2024). In addition to the currently authorized and approved treatments, FDA approved and authorized COVID-19 vaccines may provide protection to individuals against symptomatic SARS-CoV-2 infections. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include 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, see section 2).

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. (Dorabawila et al. 2022) , Israel (Bar-On et al. 2022), Qatar (Chemaitelly et al. 2022), Portugal (Kislaya et al. 2022), and England (Andrews et al. 2022). 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 Omicron BA.1 lineage descendant variant 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 BA.2-lineage descendant variants (BA.4/BA.5 and related variants) in November 2021, and based on data suggesting improved protection against Omicron BA.2-lineage descendant variants 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 with 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, 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. EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of Moderna and Pfizer-BioNTech COVID-19 vaccines (Original monovalent) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.

Compared with COVID-19 vaccines (Original monovalent), COVID-19 vaccines, Bivalent (Original and Omicron BA.4/BA.5) provided improved protection from COVID-19 caused by Omicron BA.2-lineage descendant variants, including the predominant BA.4/BA.5 variant. However, following emergence of Omicron XBB-lineage descendant variants, including the predominant XBB.1.5 variant, by April 2023, and based on data suggesting potential improved protection against XBB-lineage descendant variants conferred by monovalent XBB.1.5-based COVID-19 vaccines (2023-2024 Formula) compared with COVID-19 vaccines, Bivalent (Original and Omicron BA.4/BA.5), FDA authorized on September 11, 2023, use of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) and Moderna COVID-19 Vaccine (2023-2024 Formula) for use in individuals 6 months through 11 years of age. FDA also authorized on October 3, 2023, use of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for use in individuals 12 years of age and older. In addition, on September 11, 2023, Spikevax (COVID-19 Vaccine, mRNA) (2023-2024 Formula) and COMIRNATY (COVID-19 Vaccine, mRNA) (2023-2024 Formula) were approved for use in individuals 12 years of age and older.

The effectiveness COVID-19 vaccines (2023-2024 Formula) against more currently circulating Omicron lineages, including JN.1-lineage descendant variants, appears to wane over time (Link-Gelles 2024), suggesting that an updated composition of COVID-19 vaccines to more closely match currently circulating JN.1-lineage descendant variants is warranted for the anticipated 2024-2025 respiratory virus season in the U.S.

Effectiveness and safety data accrued with the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula) are relevant to Moderna COVID-19 Vaccine (2024-2025 Formula), because all these vaccines are manufactured using the same process. The effectiveness and safety of Moderna COVID-19 Vaccine (2024-2025 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), and from postmarketing experience.

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 (2024-2025 Formula) may be effective in individuals 6 months through 11 years of age. In addition, the nonclinical data reviewed indicate that Moderna Vaccine (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Moderna COVID-19 Vaccine (2023-2024 Formula) against JN.1-lineage descendant variants, including JN.1, KP.2, KP.3 and LA.2.

Based on the totality of the available evidence (see 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 (2024-2025 Formula) will likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the currently predominant JN.1-lineage descendant variants, compared with Moderna COVID-19 Vaccine (2023-2024 Formula).

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 data from the FDA Biologics Effectiveness and Safety (BEST) System (available only for individuals > 12 years of age), within a week after the first dose of mRNA-based COVID-19 vaccine (2023-2024 Formula), the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events in the inpatient or emergency department setting was (b)(4) cases per one million doses for persons aged 12 through 45 years (unpublished data, based on fewer than 10 cases).

Two recent studies evaluated febrile seizures among children ages 2 through 5 years of age (see section 6.1.2). In view of the findings on febrile seizures following administration of Moderna COVID-19 Vaccine described above as well as VAERS reports of febrile seizures following administration of Moderna COVID-19 Vaccine, a labeling change was made to the *Postmarketing Experience* section of the Fact Sheet for Health Care Providers Administering Vaccines and the *What are the Risks of Moderna COVID-19 Vaccine* section of Fact Sheet for Recipient and Caregivers to include *Febrile seizure* on the list of adverse reactions identified during postmarketing use.

Postmarketing evaluation of Moderna COVID-19 Vaccine (2023-2024 Formula) 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. The table below summarizes benefit-risk assessment considerations.

Table 1. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SARS-CoV-2, the causative agent of COVID-19, has caused over 100 million symptomatic cases, and, as of June 1, 2024, nearly 1.2 million deaths in the U.S.[1]	• COVID-19 can be both a serious acute disease, associated with significant morbidity and mortality, and, in a subset of individuals infected with SARS-CoV-2, a serious chronic protean disease (now defined as Long COVID).[2]
	• Original monovalent mRNA-based COVID-19 vaccines authorized in the U.S. initially had high effectiveness (90- 95% vaccine efficacy) against symptomatic disease; however, in combination with waning individual immunity, vaccine effectiveness has declined with successive emergence of parent lineage descendants of SARS-CoV-2 Variants of Concern (i.e., Beta, Delta, and most recently Omicron), despite periodic antigen updates.	• An ongoing succession of parent lineage descendants of SARS-CoV-2 Variants of Concern (i.e., Beta, Delta, and most recently Omicron) has driven the need for periodic antigen updates to restore vaccine effectiveness.
	• Trends of waning effectiveness of COVID-19 vaccines (2023-2024 Formula) against medically attended COVID-19 among individuals ≥18 years of age was prominent ≥120 days since last dose and against symptomatic infection by presumed JN.1-lineage descendant variants.[3]	• While the current COVID-19 vaccines (2023-2024 Formula) continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased in the context of currently circulating Omicron JN.1-lineage descendants and warrant updating the current formula of COVID-19 vaccines for the anticipated 2024–2025 respiratory virus season in the U.S. to more closely match currently circulating JN.1-lineage descendant variants.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Options for Treatment or Prevention of COVID-19 Disease	• Antiviral medications and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in individuals with mild to moderate COVID-19.	• Although antivirals are approved or authorized to treat individuals at high risk for progression to severe COVID-19, they are not labelled for treating severe disease or individuals who are not at high risk; additionally, the extent to which antiviral treatment may prevent Long COVID is unclear.
	• A SARS-CoV-2 spike IgG1 mAb Pemivibart (Pemgarda) injection, for intravenous use) has been authorized for *pre-exposure* prophylaxis of COVID-19 in individuals 12 years of age and older weighing at least 40 kg, who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination.	• Pemivibart (Pemgarda) is not authorized for use in individuals less than 12 years of age, nor individuals 12 years of age and older with moderate to severe immunocompromise who are likely to mount an adequate immune response to COVID-19 vaccination.
	• Currently in the U.S., there are: two authorized COVID-19 vaccines (2023-2024 Formula) for use as a 2- or 3-dose regimen in individuals 6 months through 4 years of age (yoa) and as a single-dose regimen in individuals 5 through 11 years; two approved COVID-19 vaccines (2024-2025 Formula) for use as a single-dose regimen in individuals ≥12 yoa; and an adjuvanted, protein subunit COVID-19 vaccine (2023-2024 Formula) authorized for use as 2-dose regimen in previously unvaccinated individuals and use as single-dose regimen in previously vaccinated individuals >12 yoa.	• Staying up to date on COVID-19 vaccines remains a core prevention strategy in the U.S., as vaccination significantly lowers the risk of severe morbidity and mortality from COVID-19; as such, updating the current formula of COVID-19 vaccines for the anticipated U.S. 2024-2025 respiratory virus season to more closely matching currently circulating JN.1-lineage descendant variants is warranted to potentially provide additional benefit from use of COVID-19 vaccines.[4]

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Available nonclinical data demonstrated that Moderna COVID-19 vaccine (2024- 2025 Formula), when administered to vaccine naïve- and vaccine-experienced laboratory animals, elicited higher neutralizing antibody responses against currently circulating JN.1-lineage descendant variants compared with Moderna COVID-19 vaccine (2023-2024 Formula). In addition, a human immunogenicity study of a monovalent JN.1-containing vaccine candidate suggested that a JN.1-based vaccine is likely to produce higher neutralizing antibodies to JN.1 variant and emerging JN.1-lineage descendant variants (e.g., KP.2) than an XBB.1.5-based or a related vaccine.[5]	• Given the enhanced neutralizing antibody activity against more recently circulating SARS-CoV-2 variants demonstrated in nonclinical studies of Moderna COVID-19 Vaccine (2024-2025 Formula) compared with Moderna COVID-19 Vaccine (2023-2024 Formula) and given preliminary data reported from post-vaccination and post-infection studies in humans, it is reasonable to expect that administration of Moderna COVID-19 Vaccine (2024-2025 Formula) doses may provide additional benefit compared with administration of Moderna COVID-19 Vaccine (2023-2024 Formula) doses for the anticipated U.S. 2024-2025 respiratory virus season.
	• Key residual uncertainty: whether higher neutralizing antibody responses in nonclinical studies, and in post-infection and post-vaccination studies in humans translates into improved vaccine effectiveness against COVID-19 outcomes in humans, including symptomatic and serious disease.	• The totality of the available evidence indicates it is reasonable to expect that Moderna COVID-19 Vaccine (2024- 2025 Formula) may provide additional benefit compared with Moderna COVID-19 Vaccine (2023-2024 Formula), particularly against currently circulating JN.1-lineage descendant variants.

1 CDC. About COVID-19. Factsheet. June 13, 2024.
2 NASEM report
3 Link-Gelles, R. Effectiveness of COVID-19 (2023-2024 Formula) vaccines. Presentation to ACIP, June 2024. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-06-26-28/03-COVID-Link-Gelles-508.pdf
4 CDC. COVID-19: How to protect yourself and others. Fact sheet. July 12, 2024.
5 WHO. Statement on the antigen composition of COVID-19 vaccines. April 26, 2024.

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months through 11 years of age, when considering the totality of available evidence and residual uncertainties, and when used as described in section 5.1 for all doses appropriate to age and immune status, it is reasonable to expect that the known and potential benefits of the Moderna COVID-19 Vaccine (2024-2025 Formula) outweigh the known and potential risks of the vaccine. Administration of Moderna COVID-19 Vaccine (2024-2025 Formula) is expected to have a favorable benefit-risk profile and to restore protection against serious outcomes from COVID-19, during the current wave of COVID-19 caused predominantly by JN.1-lineage descendant variants.

For individuals with certain kinds of immunocompromise turning from 11 to 12 years of age during the three-dose vaccination series, when considering the totality of available evidence, including evidence supporting licensure of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) (refer to Spikevax), and residual uncertainties, it is reasonable to expect that the known and potential benefits of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) outweigh its known and potential risks when used to complete the vaccination series in such individuals as described in section 5.1.

Furthermore, given that over one billion doses of mRNA COVID-19 vaccines have been administered worldwide, the benefit-risk assessment of mRNA COVID-19 vaccines is informed by substantial

postmarketing experience. 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 EUA Decision Memorandum dated September 11, 2023).

9 Overall Summary and Recommendations

Following review of the VRBPAC discussion and recommendations from the June 5, 2024, meeting and the Sponsor's EUA request, the Review Team considered the following in its benefit-risk assessment of the Moderna COVID-19 Vaccine (2024-2025 Formula) and certain uses of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 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 amendment includes the following:
    - Nonclinical data demonstrating that Moderna COVID-19 Vaccine (2024-2025 Formula) when administered to vaccine-naive and vaccine-experienced laboratory animals, elicited higher neutralizing antibodies compared to the Moderna COVID-19 Vaccine (2023-2024 Formula) against JN.1-lineage descendant variants,
    - Chemistry, Manufacturing and Control information related to pre-filled syringe presentation of Moderna COVID-19 Vaccine (2024-2025 Formula) including the manufacturing facilities,
    - Clinical safety, immunogenicity, and efficacy data from studies which evaluated primary and booster vaccination with the Moderna COVID-19 Vaccine (Original monovalent) and Bivalent Vaccine (Original and Omicron BA.1),
    - Observational effectiveness data from studies which evaluated primary and booster vaccination with the Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and/or Moderna COVID-19 Vaccine (2023-2024 Formula),
    - Postmarketing safety surveillance data of Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and Moderna COVID-19 Vaccine (2023-2024 Formula),
    - Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with real-world data, and
    - Data and information supporting licensure of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula).
- Although available evidence suggests that the Moderna COVID-19 Vaccine (2023-2024 Formula) continues to provide some protection in the U.S. against serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, based on the totality of available scientific evidence, it is reasonable to conclude that the Moderna COVID-19 Vaccine (2024-2025 Formula), administered as a single dose to all immunocompetent individuals (unvaccinated or vaccinated) 5 through 11 years of age at least 2 months following the last previous 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 JN.1-lineage descendant variants.

- 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 (2024-2025 Formula), administered as a two-dose series may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including JN.1-lineage descendant variants.

- 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), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) or Moderna COVID-19 Vaccine (2023-2024 Formula), it is reasonable to conclude that the Moderna COVID-19 Vaccine (2024-2025 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 JN.1-lineage descendant variants.

- 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), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) or Moderna COVID-19 Vaccine (2023-2024 Formula), it is reasonable to conclude that the Moderna COVID-19 Vaccine (2024-2025 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 JN.1-lineage descendant variants.

- 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 (2024-2025 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 JN.1-lineage descendant variants 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), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and/or Moderna COVID-19 Vaccine (2023-2024 Formula),
    - a single dose administered at least 2 months after the last previous dose of Moderna COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) or Moderna COVID-19 Vaccine (2023-2024 Formula) 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), a bivalent COVID-19 vaccine or a

COVID-19 Vaccine (2023-2024 Formula) 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 (2024-2025 Formula) in immunocompromised individuals 6 months through 4 years of age at least 2 months following the last dose of Moderna COVID-19 Vaccine (2024-2025 Formula) in at least a three-dose series in which at least 1 dose was with Moderna COVID-19 vaccine (2024-2025 Formula),
- an additional dose of Moderna COVID-19 Vaccine (2024-2025 Formula) in immunocompromised individuals 5 through 11 years of age at least 2 months following the last dose of a COVID-19 vaccine (2024-2025 Formula) in at least a three-dose series in which at least 1 dose was with a COVID-19 vaccine (2024-2025 Formula), and
- age-appropriate additional doses of Moderna COVID-19 Vaccine (2024-2025 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 (2024-2025 Formula) is supported by a combination of clinical studies and real-world evidence.
- Based on the totality of available scientific evidence, it is reasonable to conclude that administration one or two doses(s), as applicable, of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) in individuals with certain kinds of immunocompromise turning from 11 to 12 years of age during the three-dose vaccination series in order to complete the series on or after the date the individual turns 12 years of age may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including JN.1-lineage descendant variants.
- 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, it is reasonable to expect that the known and potential benefits of the Moderna COVID-19 Vaccine (2024- 2025 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.
- Based on FDA's review of the available scientific evidence, including the evidence described in section 6 and the data and information supporting licensure of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula), it is reasonable to conclude that the known and potential benefits of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) outweigh its known and potential risks when used in individuals with certain kinds of immunocompromise turning from 11 to 12 years of age during the three-dose vaccination series in order to complete the series on or after the date the individual turns 12 years of age.
- Known and potential benefits of the Moderna COVID-19 Vaccine (2024-2025 Formula) and the uses of Spikevax (2024-2025 Formula) under consideration for this EUA amendment include reduction in the risk of COVID-19 and associated serious sequelae, including from COVID-19 due to JN.1-lineage descendant variants.

- 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 febrile seizures), 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 (2023-2024 Formula) in the U.S.; 2) revision of the EUA to provide for use of the Moderna COVID-19 Vaccine (2024-2025 Formula) administered in an appropriate schedule based on age and immune status, as reflected in the Fact Sheets; and 3) revision of the EUA to provide for use of Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) in individuals with certain kinds of immunocompromise turning from 11 to 12 years of age during the three-dose vaccination series in order to complete the series on or after the date the individual turns 12 years of age.

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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

Body System/Classification Adverse Event of Special Interest	Estimated Risk Window (Days)
Transverse myelitis[1]	1-42
Bell's palsy	1-42
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-like 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 described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.