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

Application Type	EUA Amendment
Application Number	EUA 28237, Amendment 246-275
Sponsor	Novavax, Inc.
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Review Completion Date	August 30, 2024
Established Name/Names used during development	Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)
Dosage Forms/Strengths and Route of Administration	0.5 mL suspension for intramuscular injection (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 12 years of age and older

Table of Contents

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).

Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is a nanoparticle vaccine that contains prefusion stabilized full-length recombinant spike (S) protein of the Original (Wuhan Hu-1) SARS-CoV-2 strain, hereafter referred to as Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). It also contains Matrix-M adjuvant comprised of saponins derived from the soapbark tree (*Quillaja saponaria Molina*). As SARS-CoV-2 evolved, the Novavax COVID-19 vaccine formula has been updated. On October 3, 2023, FDA authorized the use of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older with a dosing schedule based on vaccination status, including additional doses for individuals with certain kinds of immunocompromise. For more details on the composition and authorizations of Novavax COVID-19 Vaccine, Adjuvanted, (Original monovalent) and Novavax COVID-19, Adjuvanted (2023-2024), please refer to Novavax COVID-19 Vaccine, Adjuvanted, Decision Memos and Regulatory Documents and EUA Decision Memorandum Dated October 3, 2023, respectively.

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. Novavax Inc.,

on June 13, 2024, requested authorization of their COVID-19 vaccine to include a monovalent JN.1-based 2024-2025 Formula.

The clinical effectiveness data accrued with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), Novavax's adjuvanted monovalent COVID-19 Vaccine (Omicron BA.5)[1] hereafter referred to as monovalent vaccine (Omicron BA.5), and Novavax's adjuvanted monovalent COVID-19 Vaccine (Omicron BA.1)[1], hereafter referred to as monovalent vaccine (Omicron BA.1), are relevant to the effectiveness of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because these vaccines are manufactured using a similar process. The clinical safety data accrued with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), monovalent vaccine (Omicron BA.1), Novavax's adjuvanted bivalent vaccine (Original and Omicron BA.1)[1], hereafter referred to as bivalent vaccine (Original and Omicron BA.1), and Novavax's adjuvanted bivalent vaccine (Original and Omicron BA.5)[1], hereafter referred to as bivalent vaccine (Original and Omicron BA.5), are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because these vaccines are manufactured using a similar process.

The effectiveness and safety of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is based on the totality of evidence from clinical trials, including efficacy and effectiveness data with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and immunogenicity data of the monovalent vaccine (Omicron BA.1) and monovalent vaccine (Omicron BA.5).

Post-authorization effectiveness and safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), were considered relevant to the effectiveness and safety evaluation and benefit-risk assessment of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is manufactured using a similar process as Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Review of post-authorization safety data indicate a similar safety profile of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)

Cumulative global data submitted by the Sponsor indicated distribution of (b) (4) doses of all Novavax COVID-19 vaccine, Adjuvanted formulations in all ages as of July 31, 2024, including (b) (4) doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). In the Sponsor global safety database, cumulatively through July 31, 2024, the Sponsor received 5,682 individual case safety reports (ICSRs) representing 20,359 cases of adverse events specifically in individuals who received any Novavax 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 Novavax COVID-19 Vaccine, Adjuvanted vaccine formulations in individuals 12 years of age and older, including (b) (4) doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). The most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were: headache, dizziness, fatigue, pyrexia, chest pain, dyspnea, myalgia, nausea, pain, and pain in extremity. The Sponsor is also conducting post-authorization studies to evaluate the association between the Novavax COVID-19 Vaccine, Adjuvanted 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 Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), and certain other Novavax COVID-19 vaccines, are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2024-

[1] Not authorized or approved in the U.S.

2025 Formula) because all these vaccines are manufactured using a similar process. In addition, the nonclinical data reviewed indicate that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Novavax COVID-19 Vaccine, Adjuvanted (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 12 years of age and older, the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) compared with Novavax COVID-19 Vaccine, Adjuvanted (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.

Although approved KP.2-based mRNA vaccines are available, to provide additional preventative options that use alternative manufacturing technologies (e.g., an adjuvanted, protein subunit COVID-19 vaccine) while addressing 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) based on the totality of scientific evidence available, including relevant clinical effectiveness and safety evidence from previous Novavax COVID-19 vaccines, Adjuvanted manufactured using a similar process. This authorization would provide an alternative to mRNA-based COVID-19 vaccines for individuals 12 years of age and older.

Taken together, the Review Team recommends: 1) discontinuation of the authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula); and 2) authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals 12 years of age, with an appropriate dosing schedule based on previous vaccination status and immune status.

In addition, as discussed in section 7.1, based on the totality of product stability data available through August 28, 2024, the Sponsor proposed a nominal initial 3-month shelf life for Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) distributed in the U.S. after authorization. Given the remaining uncertainties on the ultimate stability of the product (see 7.1), FDA will require the Sponsor to use an agreed-upon relative potency lower release limit specification and submit for agency review: 1) 1-month stability (relative potency) data before distribution of initial commercial lots; and 2) real-time monthly stability (relative potency) data for all vaccine lots distributed for commercial use in the U.S. under the EUA.

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 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 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 Sheets. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) are detailed in the decision memorandum available on the FDA Website.

2.2.2 Spikevax (COVID-19 Vaccine, mRNA) (2024-2025 Formula) and Moderna COVID-19 Vaccine (2024-2025 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 (2024-2025 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 through 11 years of age, a 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 (2024-2025 Formula) Fact Sheets. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine (2024-2025 Formula) are detailed in the decision memorandum available on the FDA Website.

2.2.3 Comirnaty (2024-2025 Formula) and Pfizer-BioNTech COVID-19 Vaccine, (2024-2025 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 (2024-2025 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 through 11 years of age, a three-dose regimen in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, a 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 or more 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 (2024-2025 Formula) Fact Sheets. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are detailed in the decision memorandum 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 authorized for use only when only when the combined national frequency of variants with substantially reduced susceptibility to Pemgarda is less than or equal to 90%, based on available information including variant susceptibility to Pemgarda and national variant frequencies. 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; Mateo-Uridales et al. 2023) 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, Novavax had evaluated "at-risk" a JN.1 candidate vaccine prototype (i.e., JN.1) 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 adjuvanted, protein subunit COVID-19 vaccines. Novavax indicated that, given these timing considerations, if VRBPAC "recommendation precludes use of a JN.1 vaccine, protein-based vaccine will not be available for Fall campaign" (see slide CO-18, Vaccines and Related Biological Products Advisory Committee June 5, 2024 Meeting Presentation- Novavax Data in Support of 2024-2025 Vaccine)."

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 Novavax COVID-19 Vaccine, Adjuvanted

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), Novavax Inc., requested, on June 13, 2024, authorization of their COVID-19 vaccine to include a monovalent JN.1-based 2024-2025 Formula with the same dose and administration schedule authorized for Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Novavax's request was supported by the following information:

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

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 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) and to Remove Authorization of the Novavax COVID-19 Vaccine, Adjuvanted for Export

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 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) to protect the public health. As outlined in section 1, the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is authorized for use in individuals 12 years of age and older. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), for individuals 12 years of age and older, 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). 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 Novavax'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 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for use in the U.S. is appropriate to protect the public health.

The current EUA also authorizes the export of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), subject to certain 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 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) and Novavax COVID-19 Vaccine (Original monovalent) 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 data accrued with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), and monovalent vaccine (Omicron BA.1), and the clinical safety data accrued with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.1), and bivalent vaccine (Original and Omicron BA.5), are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because these vaccines are manufactured using a similar process. For details of previously reviewed data that support the clinical effectiveness and safety of Novavax COVID-19 Vaccine (2024-2025 Formula) for individuals 12 years of age and older, please refer to EUA Decision Memorandum Dated October 3, 2023.

6.1.1 Immunocompromised Individuals

The safety and effectiveness of additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) for individuals 12 years of age and older with certain kinds of immunocompromise is based on the same evidence for use of additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for such individuals, as described in section 6 of the EUA Decision Memorandum Dated October 3, 2023.

6.1.2 Conclusion

Previously reviewed data support the clinical effectiveness and safety of Novavax COVID-19 Vaccine (2024-2025 Formula) for individuals 12 years of age and older (please refer to EUA Decision Memorandum Dated October 3, 2023). The effectiveness and safety of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is based on the totality of evidence from clinical trials, including efficacy and effectiveness data with the Novavax COVID-19 Vaccine, Adjuvanted (Original

monovalent) and immunogenicity data of the monovalent vaccine (Omicron BA.1) and monovalent vaccine (Omicron BA.5) and additional safety data reviewed in section 6.2 below.

It is reasonable to expect from extrapolation of immunogenicity in individuals 12 through 17 years of age and from inference of efficacy and immunogenicity in individuals 18 years of age that Novavax COVID-19 Vaccine COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may be effective in individuals 12 years of age and older. In addition, the nonclinical data reviewed indicate that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) against JN.1-related descendant variants.

Consequently, to address the urgent public health need for COVID-19 vaccines more closely matched to circulating SARS-CoV-2 variants and to provide additional preventative options that use alternative manufacturing technologies (e.g., an adjuvanted, protein subunit COVID-19 vaccine), FDA considers it appropriate to authorize the emergency use of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) for individuals 12 years of age and older based on the totality of scientific evidence available, including relevant clinical effectiveness and safety evidence from previous Novavax COVID-19 vaccines, Adjuvanted manufactured using a similar process.

6.2 Additional Safety Data

Given that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is manufactured using a similar process as Novavax COVID-19 Vaccine (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), cumulative post-authorization safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) were considered relevant to the comprehensive safety evaluation of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula).

6.2.1 Post-authorization Safety

Review of post-authorization safety data indicate a similar safety profile of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (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 July 31, 2024, including (b) (4) doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). In the global safety database, cumulatively through July 31, 2024, the Sponsor received 5,682 ICSRs representing 20,359 cases of adverse events (AEs) in individuals who received any Novavax COVID-19 vaccines, Adjuvanted. Of these, 598 (80.9%) ICSRs were non-serious,1084 (19.1%) ICSRs were serious, and 43 ICSRs (0.8%) reported a fatal outcome. Of the 5,682 cumulative ICSRs, 521 (9.2%) ICSRs involved the 2023-2024 Formula. Of these 521 ICSRs, 72 (13.8%) were serious and 8 (1.5%). fatalities were reported.

Cumulative U.S. data submitted by the Sponsor indicated distribution of (b) (4) doses of all Novavax COVID-19 vaccines, Adjuvanted in individuals 12 years of age and older including (b) (4) doses of Novavax COVID-19 Vaccine (2023-2024 Formula). The Vaccine Adverse Event Reporting System (VAERS) was queried for AE reports following all doses of Novavax COVID-19 vaccines (i.e., Original monovalent and 2023-2024 Formula) among individuals 12 years of age and older. As of August 26, 2024, there were 924 events, of which 532 (57.6%) were reported as serious and 32 (3.5%) involved a fatality. All death reports were individually reviewed. There were no reports of deaths that were attributed to Novavax COVID-19 vaccines, Adjuvanted based on

FDA medical review of the cases. The most frequently reported preferred terms (PTs) were: headache, dizziness, fatigue, pyrexia, chest pain, dyspnea, myalgia, nausea, pain, and pain in extremity.

For important risks identified in the pharmacovigilance plan for Novavax COVID-19 vaccines, Adjuvanted, anaphylaxis and myocarditis/pericarditis are identified risks that are included in the EUA Fact Sheets. The Sponsor is conducting a safety related post-authorization study for Novavax COVID-19 Vaccine, Adjuvanted, to evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is manufactured using the same baculovirus/Sf-9 insect cell platform, production scale, and manufacturing site used for the manufacturing of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). The Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) contains a recombinant full-length spike glycoprotein (rS) of the JN.1-lineage descendant JN.1 variant. The JN.1 rS is expressed from a recombinant baculovirus vector in *Spodoptera frugiperda* (Sf9) insect cells, purified by (b) (4) chromatography and formulated in a buffer containing sodium phosphate, sodium chloride, and polysorbate 80. The drug product (DP) is a co-formulation of the JN.1 rS drug substance (DS) with a saponin-based Matrix-M adjuvant derived from the soapbark tree (*Quillaja saponaria* Molina) and formed into matrix particles with phosphatidylcholine and cholesterol.

Analytical comparability assessment of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DS lots manufactured at the (b) (4) showed comparable product quality. The Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) DS is manufactured at (b) (4) scales.

There have been no major changes to the CMC information for the Matrix-A and Matrix-C adjuvant components authorized under the original EUA 28237.

The analytical methods for the assessment of critical quality attributes (identity, purity, quality, and potency) of the DS and DP for product release and stability evaluation have been qualified/validated for performance and met pre-specified acceptance criteria for accuracy, inter- and intra-assay precision, specificity, and sensitivity, and are suitable for their intended use.

Change in presentation: The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DP were authorized as multi-dose vial (MDV) presentation. The Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) DP is formulated at (b) (4) scale and filled in pre-filled syringes (PFS). The (b) (4) DP/PFS manufacturing process was originally validated for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) with the manufacture of 3 process performance qualification (PPQ) lots at commercial scale. A comprehensive analytical comparability assessment of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) showed comparable product quality of the authorized 5-dose MDV presentation and a PFS presentation, which was never authorized under this EUA.

DS stability: The shelf life for rS DS storage of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) at (b) (4) is (b) (4) Based on the similarity in the DS manufacturing process, composition (excipients), storage

temperature (b) (4) and comparable analytical quality of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) DS and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DS, the proposed initial (b) (4) shelf-life at (b) (4) for DS storage of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is deemed appropriate. The shelf-life can be further extended with real-time stability data, when available.

DP stability: The shelf life for DP storage of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in MDV presentations at 2-8°C is 9 months. Although the manufacturing process, composition (excipients), storage temperature (2-8°C), and analytical quality of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DP are similar and comparable to the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), the available real-time stability data for relative potency for the PFS PPQ lots of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) (up to 6-month data) and the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (up to 3-month data), stored at 2-8°C did not support the (b) (4) shelf-life originally requested by the Sponsor.

Based on the totality of product stability data submitted by the Sponsor through August 28, 2024, the Sponsor proposed to use a nominal initial 3-month shelf life for DP that would be distributed in the U.S. after authorization. Given the remaining uncertainties on the ultimate stability of the product, FDA will require the Sponsor to use an agreed-upon relative potency lower release limit specification and submit for agency review 1-month stability data before distribution of the initial commercial lots and submit real-time monthly stability (relative potency) data for all vaccine lots distributed under the EUA. FDA will also revise the letter of authorization (LOA) to include certain requirements related to product stability, such as requirements to ensure that the Sponsor takes appropriate action with respect to any lot that does not meet the relative potency lower release limit specification or if FDA raises objections to the distribution or use of any lot based on the monthly stability data findings (see LOA Condition J).

In addition, the Sponsor will submit the Certificates of Analysis of DP lots to be distributed under the EUA for review, at least 48 hours prior to lot distribution in the U.S.

7.2 Facilities

The manufacture of the Novavax COVID-19 Vaccine, Adjuvanted, (2024-2025 Formula) in pre-filled syringe (PFS) presentation is performed at existing facilities that were previously included in the EUA for the manufacture of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). These facilities are included in the EUA request for the manufacture of the authorized 5 µg/dose of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). Two new drug product release testing facilities were introduced. A new aseptic filling line in Building (b) (4) is added for PFS drug product manufacture in (b) (4) (b) (4) No additional changes were made to the facilities, support equipment, quality systems and controls. An on-site inspection for the new syringe filling line was performed on (b) (4) FDA finds that all facilities within the scope of this authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) are adequate to support the use of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) under an EUA.

7.3 Nonclinical Studies

Nonclinical studies were completed in mice to evaluate immunogenicity of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) given as a two-dose primary series or as a booster. The submitted results demonstrated that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) vaccine elicited strong neutralizing antibody responses against variant JN.1 and other JN.1-lineage

descendant variants, including but not limited to JN 1.7, KP.2, LA.2, and KP.3 after primary and booster vaccinations compared with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). These data are therefore considered supportive for the formula change to Omicron JN.1-lineage variant JN.1 for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula).

7.4 Pharmacovigilance Activities

In addition to adverse event reporting, Novavax is conducting safety-related post-authorization studies for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Novavax has a pharmacovigilance plan (PVP) (version 2.5 dated June 5, 2024) to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). The PVP includes the following:

- Important Identified Risks: Anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)
- Missing Information: Use in pregnancy and while breastfeeding; use in immunocompromised patients; use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders); use in patients with autoimmune or inflammatory disorders; interaction with other vaccines; and long-term safety

Compared to the pharmacovigilance plan (PVP) for the 2023-2024 Formula (Version 2.4, dated September 29, 2023), the safety concerns in the pharmacovigilance plan for the 2024-2025 Formula are unchanged. No safety signals have been identified since the last reviewed PVP and no clinical safety data was included in this submission. Therefore, the currently available safety data do not suggest a need for a change in the PVP.

7.4.1 Sponsor Pharmacovigilance Activities

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

- VAERS reporting: Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); myocarditis; pericarditis; Multisystem Inflammatory Syndrome; COVID-19 resulting in hospitalization or death. In addition, FDA requested that Novavax submit all reports of “Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)” (regardless of seriousness) to VAERS within 15 days of receipt.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether associated with an AE; newly identified safety concerns; and cumulative and interval doses distributed.
- Post-authorization observational studies will evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and cases of COVID-19 resulting in hospitalization. The studies below are being conducted for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent and 2023-2024 Formula) in large-scale databases and will include a sub-analysis for Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). This condition of authorization under the EUA, to conduct post-authorization

observational studies, will encompass the evaluation of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in authorized age groups in the following studies:

- **Study 2019nCoV-405**: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

  - Objective: To estimate the risk of obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women 18 years of age and older exposed to single (homologous) or mixed (heterologous) Novavax COVID-19 vaccine series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccines during pregnancy.

- **Study 2019nCoV-404**: U.S. Post-authorization Safety Study Using a Claims Database

  - Objective: To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted in individuals 12 years of age and older in the U.S. using a self-controlled case series (SCCS) design.

- **Study 2019nCoV-402**: UK Post-Authorization Safety Study Using the Clinical Practice Research Datalink

  - Objective: To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted in individuals 12 years of age and older in England using a self-controlled case series (SCCS) design (i) a SCCS design and (ii) a comparative cohort design.

As per FDA request, Novavax added “Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)” as a safety outcome in their ongoing post authorization safety studies.

Additionally, the Sponsor is conducting the following effectiveness studies:

- **Study 2019nCoV-403**: U.S. Post-Authorization Effectiveness Study Using a Claims Database

  - Objective: To estimate the effectiveness of the Novavax COVID-19 Vaccine in preventing COVID-19 hospitalizations compared to unvaccinated individuals.

- **Study 2019nCoV-401**: EU/EEA Post-Authorization Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform

  - Objective: To estimate vaccine effectiveness of Novavax COVID-19 Vaccine against hospitalization due to laboratory-confirmed SARS-CoV-2 in patients with severe acute respiratory infection.

7.4.2 Additional Sponsor Post-Authorization Effectiveness Study

The Sponsor will be required to conduct the following post-authorization effectiveness study to evaluate the effectiveness of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in preventing COVID-19 disease caused by antigenically distinct variants of SARS-CoV-2 that may emerge in the future.

- **Study 2019nCOV-315:** Post-authorization clinical study to evaluate immune responses after a one-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) according to the following schedule:

  - Final Protocol Submission: September 30, 2024
  - Topline Results Submission: February 28, 2025
  - Study Completion Date: May 31, 2025
  - Final Study Report Submission: August 31, 2025

The Sponsor will submit the protocol, results, and final study report to IND 22430.

7.4.3 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 dosage and administration information provided in the Fact Sheets was revised to enhance clarity of the dosing schedule for individuals 12 years of age and older vaccinated only with one dose of any Novavax COVID-19 Vaccine, Adjuvanted.

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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in Individuals 12 years 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. For disease prevention in individuals 12 years of age and older, there are approved mRNA-based COVID-19 vaccines from Moderna and Pfizer-BioNTech (see section 2) and a currently authorized adjuvanted, protein subunit COVID-19 vaccine from Novavax. For disease prevention in individuals 6 months of age and older, there are authorized mRNA-based COVID-19 vaccines from Moderna and Pfizer-BioNTech (see section 2).

The original monovalent COVID-19 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.

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), FDA approved on September 11, 2023, Spikevax (COVID-19 Vaccine, mRNA) (2023-2024 Formula) and COMIRNATY (COVID-19 Vaccine, mRNA) (2023-2024 Formula) and authorized on October 3, 2023, Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for use in individuals 12 years of age and older. In addition, FDA authorized on September 11, 2023, 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.

The effectiveness of 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.

As summarized in section 3.2 above, the evidence presented to VRBPAC, including nonclinical data generated from "at-risk" COVID-19 candidate vaccines, did not definitively point to an advantage of selecting a specific variant (e.g., JN.1 or KP.2) for inclusion in 2024-2025 Formula. Based on the most current available data following the VRBPAC meeting, along with the rise in cases of COVID-19 in areas of the country, the agency determined that the preferred JN.1-lineage for the COVID-19 vaccines (2024-2025 Formula) is the KP.2 strain, if feasible. Nevertheless, the nonclinical data presented by Novavax at VRBPAC (see VRBPAC Meeting Novavax Presentation) and the nonclinical data submitted to FDA as part of the EUA request (see section 7.3) demonstrated that their JN.1-based COVID-19 candidate vaccine, elicited significant neutralizing antibodies against JN.1-lineage descendant variants, including JN.1, KP.2, LA.2, and KP.3.

Although approved KP.2-based mRNA vaccines are available, to provide additional preventative options that use alternative manufacturing technologies (e.g., an adjuvanted, protein subunit COVID-19 vaccine) while addressing 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). This authorization is based on relevant clinical effectiveness and safety evidence from previous Novavax COVID-19 vaccines, Adjuvanted manufactured using a similar process and the previously-discussed data (addressed in sections 6 and 7) supporting the likelihood that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) will increase immune responses and protection against COVID-19 caused by SARS- CoV-2 variants, including currently predominant JN.1-lineage descendant variants. This authorization would provide an alternative to mRNA-based COVID-19 vaccines for individuals 12 years of age and older, including for individuals who have contraindications to the approved mRNA-based vaccines.

Effectiveness and safety data accrued with previous Novavax COVID-19 vaccines, Adjuvanted are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because all these vaccines are manufactured using a similar process. The effectiveness and safety of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is based on the totality of evidence from clinical trials and post-authorization experience.

Based on the totality of the available evidence (see sections 6 and 7), it is reasonable to expect in immunocompetent and immunocompromised individuals 12 years of age and older that the Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula).

In addition, as discussed in section 7.1, based on the totality of product stability, the sponsor proposed to use a nominal initial 3-month shelf life for DP that would be distributed in the U.S. after authorization. Given the remaining uncertainties on the ultimate stability of the product, FDA will require the Sponsor to use an agreed-upon relative potency lower release limit specification and submit for agency review 1-month stability (relative potency) data before distribution commercial lots and submit real-time monthly stability (relative potency) data for all vaccine lots distributed for commercial use in the U.S. under the EUA.

Post-authorization evaluation of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) has not suggested new safety concerns additional to the safety profile of originally authorized Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Post-deployment monitoring for adverse events using both passive and active surveillance systems will be used to assess whether any new safety concerns emerge. Table 1 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 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 (2024-2025 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), when administered to vaccine-experienced laboratory animals, elicited higher neutralizing antibody responses against currently circulating JN.1-lineage descendant variants compared with Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) compared with Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) doses may provide additional benefit compared with administration of Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may provide additional benefit compared with Novavax COVID-19 Vaccine, Adjuvanted (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 12 years of age and older, it is reasonable to expect that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) outweigh the known and potential risks of the vaccine, when used as described in Fact Sheet for Healthcare Providers Administering Vaccine, considering the totality of available evidence and the outstanding uncertainties. Administration of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is expected to have a favorable benefit-risk assessment 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.

FDA's previous benefit-risk assessments of COVID-19 vaccines, 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 October 3, 2023.

Although approved KP.2-based mRNA vaccines are available, to provide additional preventative options that use alternative manufacturing technologies (e.g., an adjuvanted, protein subunit COVID-19 vaccine) while addressing 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). This authorization would provide an alternative to mRNA-based COVID-19 vaccines for individuals 12 years of age and older.

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 Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) when administered to vaccine-experienced laboratory animals, elicited higher neutralizing antibodies compared to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) against JN.1-lineage descendant variants,

    - Chemistry, Manufacturing and Control information related to the pre-filled syringe presentation of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) including the vaccine stability and the manufacturing facilities,

    - Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated a 2-dose series in individuals 12 years of age and older previously not vaccinated with a COVID-19 vaccine and a single-dose regimen with the Novavax COVID-19 Vaccine, Adjuvanted (including Original monovalent and four modified Novavax COVID-19, Vaccine, Adjuvanted formulations containing Omicron sublineage components) in individuals 12 years of age and older previously vaccinated with a COVID-19 vaccine,

    - Post-authorization safety surveillance data of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), and

    - Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with real-world data.

- Based on the totality of available scientific evidence, in immunocompetent individuals 12 years of age and older *never vaccinated with any COVID-19 vaccine*, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), administered as a series of two doses 3 weeks apart, 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 12 years of age and older *vaccinated only with one dose of any Novavax COVID-19 Vaccine, Adjuvanted*, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), administered as a single dose at least 3 weeks after the previous dose to complete the two-dose series of Novavax COVID-19 Vaccine, Adjuvanted, 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 12 years of age and older *vaccinated with any COVID-19 vaccine, other than Novavax COVID-19 Vaccine, Adjuvanted, or with two or more doses of Novavax COVID-19 Vaccine, Adjuvanted*, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), administered as a single dose at least 2 months after receipt of the last previous dose of COVID-19 vaccine, 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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals with certain kinds of immunocompromise 12 years of age and older, 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:
  - an additional dose administered at least 2 months following the last dose of a COVID-19 vaccine (2024-2025 Formula), and
  - additional doses of Novavax COVID-19 Vaccine, Adjuvanted (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 Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is supported by a combination of clinical studies and real-world evidence.

- Based on FDA's review of the available scientific evidence, including the data summarized in section 6 and assessment of benefits and risks in section 8 of this review, it is reasonable to expect that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2024- 2025 Formula) outweigh the known and potential risks when used appropriate to previous vaccination and immune status for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

- Known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) include reduction in the risk of COVID-19 and associated serious sequelae, including from COVID-19 caused by 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, 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) discontinuation of use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula); and 2) use of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals 12 years of age, with an appropriate dosing schedule based on previous vaccination status and immune status.

In addition, as discussed in section 7.1, based on the totality of product stability, the sponsor proposed to use a nominal initial 3-month shelf life for Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) that would be distributed in the U.S. after authorization. Given the remaining uncertainties on the ultimate stability of the product (see 7.1), FDA will require the Sponsor to use an agreed-upon relative potency lower release limit specification and submit for agency review 1-month stability (relative potency) data before distribution commercial lots and submit real-time monthly stability (relative potency) data for all vaccine lots distributed for commercial use in the U.S. under the EUA.

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11 Appendices

Appendix A. Adverse Events of Special Interest

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

Body System/Classification Adverse Event of Special Interest	Estimated Risk Window (Days)
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. 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 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.	

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.