

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

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 28237.80
Sponsor	Novavax Inc.
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Review Completion Date	October 19, 2022
Established Name/Other names used during development	Novavax COVID-19 Vaccine, Adjuvanted/ NVX-CoV2373
Dosage Forms/Strengths and Route of Administration	A 0.5 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Use as a first booster dose administered at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 Vaccine
Intended Population for Booster dose	Individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.

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Glossary

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	adverse reaction
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
GMT	geometric mean titer
HHS	US Department of Health and Human Services
ICSR	Individual Case Safety Report
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MN ₅₀	microneutralization assay with an inhibitory concentration of 50%
MRI	magnetic resonance imaging
NP	nucleocapsid protein
NSTEMI	non-ST elevation myocardial infarction
NT ₅₀	50% neutralizing antibody titer
NT ₈₀	80% neutralizing antibody titer
NVX-CoV2373	Novavax COVID-19 Vaccine, Adjuvanted
O/E	observed-to-expected
PCR	polymerase chain reaction
PP-IMM	Per-Protocol Immunogenicity Analysis Set
PT	preferred term
PVNA	pseudotype virus neutralization assay
RR	reference range
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCR	seroconversion rate
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
ULN	upper limit of normal
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine effectiveness
VOC	variant of concern

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1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of October 12, 2022, has led to over 622 million cases of COVID-19 and 6.5 million deaths worldwide.¹ In the US, more than 96 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).

The Novavax COVID-19 Vaccine, Adjuvanted, also referred to as NVX-CoV2373, is a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant. NVX-CoV2373 is currently authorized for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older as a two-dose primary series of 5 µg recombinant spike protein and 50 µg of Matrix-M adjuvant administered 3 weeks apart. On July 13, 2022, FDA authorized the Novavax COVID-19 Vaccine, Adjuvanted for use under emergency use authorization (EUA) as a primary series for individuals 18 years of age and older. The EUA was amended on August 19, 2022, to include use of Novavax COVID-19 Vaccine, Adjuvanted as a primary series in individuals 12 through 17 years of age.

On August 12, 2022, FDA received a request from Novavax Inc. (the Sponsor) to amend the EUA for the Novavax COVID-19 Vaccine, Adjuvanted to include a booster dose (one dose of Novavax COVID-19 Vaccine, Adjuvanted) in individuals 18 years of age and older 6 months after completion of a primary vaccination series with NVX-CoV2373 (homologous booster) or with another authorized or approved monovalent COVID-19 vaccine (heterologous booster). As of March 26, 2022, a total of 12,738 participants 18 years of age and older received a booster dose of NVX-CoV2373 following completion of a primary series in the booster portion of an ongoing Phase 3 safety, immunogenicity, and efficacy study (Study 2019nCoV-301, referred to as Study 301). The EUA amendment included safety data and immunogenicity data assessed against the reference strain (USA_WA1/2020, Wuhan-like) from a selected subset of 298 adult participants 18 years of age and older who received a booster dose of NVX-CoV2373 at least 6 months after completion of the 2-dose homologous primary series. The amendment also included exploratory immunogenicity data against Omicron sublineages in a smaller subset of Study 301 participants, a literature report that describes immunogenicity and safety data following a booster dose of NVX-CoV2373 in 114 participants who received a 2 dose primary series of Pfizer-BioNTech COVID-19 Vaccine, and additional safety data from 12,738 booster dose recipients enrolled in Study 301.

The effectiveness of the booster dose is inferred based on immunobridging analyses using prespecified non-inferiority criteria to compare the geometric mean titer (GMT) ratio and difference in seroconversion rates (SCRs) between a subset of Phase 3 NVX-CoV2373 booster dose recipients post-booster and a subset of Phase 3 NVX-CoV2373 primary series recipients post-primary series, using a microneutralization assay with an inhibitory concentration of 50% (MN₅₀). Immunobridging analyses included hypothesis testing for:

- Geometric mean titer (GMT) ratio of SARS-CoV-2 neutralizing antibodies at 28 days after the booster dose vs. those values 14 days after the primary series, using a 0.67 non-inferiority margin, i.e., the lower bound of the 95% confidence interval around the ratio of GMTs needs to be >0.67. Additionally, the point estimate of the ratio of GMTs should be >0.83.
- Percentage of participants with seroconversion (≥4-fold rise from baseline at 28 days after the booster dose relative to time of booster and ≥4-fold rise from baseline 14 days after the

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primary series relative to time of first dose), using a -10% non-inferiority margin as the success criterion for the lower bound of the confidence interval around the difference between SCRs.

Immunobridging analyses against the reference strain met the pre-specified success criteria for GMT ratio (3.4; 95% CI: 2.8, 4.0) but not in the difference in SCRs for the booster dose compared to the 2-dose primary series (-9.2%; 95% CI: -14.4%, -4.5%). An additional descriptive post hoc analysis evaluated SCRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. The booster dose SCR, with seroconversion defined as at least a 4-fold rise relative to the time of first dose, was 98.3%. The difference in SCRs in this post-hoc analysis was 3.8% (95% CI 2.0%, 7.0%). Additional descriptive exploratory immunogenicity data evaluating neutralizing antibody titers elicited by the booster dose against the reference strain (wild-type) of SARS-CoV-2 and Omicron variant sublineages demonstrated increases in titers following a booster dose of NVX-CoV2373.

In the literature report describing immunogenicity data following a booster dose of NVX-CoV2373 in 114 participants who received a 2 dose primary series of Pfizer-BioNTech COVID-19 Vaccine, the normalized 80% neutralizing antibody titer (NT₈₀) GMT was 1,454 after a NVX-CoV2373 booster dose, compared to a GMT of 531 in the control group (non-COVID-19 active vaccine comparator) using a live virus assay (geometric mean ratio [GMR] 2.65). Using a pseudotype virus neutralizing assay, the 50% neutralizing antibody titer (NT₅₀) (Delta) GMT was 766 after a NVX-CoV2373 booster, compared with a GMT of 157 in the control group (GMR 5.39).

Safety analyses in the subset of 298 participants included evaluation of solicited local and systemic adverse reactions within 7 days after a booster dose and nonserious unsolicited adverse events (AEs) within 28 days after a booster dose. Safety analysis also included evaluation of serious adverse events (SAEs) and adverse events of special interest (AESIs) in a larger cohort of participants who received a booster dose (n=12,738) following completion of a primary series, with a median follow-up of 121 days post-booster dose (through a data extraction date of August 18, 2022). The safety follow-up is ongoing.

Solicited safety data from booster recipients (238 participants with recorded solicited reaction information) were reviewed and compared to safety data from recipients of the 2-dose primary series. Overall, local and systemic reactogenicity events were reported by a larger proportion of participants following a booster dose compared to both primary series doses. Unsolicited safety data were available from 298 booster dose recipients; unsolicited AEs were infrequent, and no new patterns of AEs were seen.

AESIs (e.g., autoimmune diseases and myocarditis) and SAEs following a booster dose were reviewed for 12,738 booster dose recipients. SAEs were reported by 1.4% of booster dose recipients. Four events were considered possibly related to the booster dose of NVX-CoV2373, including myocarditis, autoimmune hepatitis, injection site cellulitis, and events of deep vein thrombosis and pulmonary embolism in a single participant. An additional event of muscle edema was reported after the data extraction date and was also considered possibly related to a booster dose of NVX-CoV2373. Eight deaths were reported following the booster dose, all of which were assessed as unrelated to study vaccination.

Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an

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EUA for a COVID-19 vaccine after determining that certain statutory requirements are met (Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)). Considering the statutory requirements and the totality of data available at this time to inform an assessment of benefits and risks, the review team concludes that the data support the use of a Novavax COVID-19 Vaccine, Adjuvanted booster dose as a first booster dose in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. For these individuals, a booster dose (0.5 mL) of Novavax COVID-19 Vaccine, Adjuvanted may be administered at least 6 months after completion of a primary vaccination with an authorized or approved COVID-19 vaccine.

2. Background

2.1. SARS-CoV-2 Virus and COVID-19 Disease

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with variable respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions,² may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome, leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks but symptoms may persist for months in some individuals.³ Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults but are generally milder, with fever and cough most commonly reported.^{4,5} Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.⁴

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 18, 2022, has led to over 625 million cases of COVID-19 and 6.5 million deaths worldwide.¹ In the US, more than 96 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).⁶ Over 82% of US cases occurred in adults greater than 18 years of age. Individuals 50 years of age and older accounted for 93.1% of deaths due COVID-19.⁷

Since the start of the pandemic caused by the Wuhan strain of SARS-CoV-2 (also referred to as the ancestral, original, or reference strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron (B.1.1.529). The Omicron variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including the recent BA.4 and BA.5, which account for nearly all reported COVID-19 cases in the US currently, that have been associated with recent increases in COVID-19 case rates.⁸ In addition, population-level evidence suggests an increased reinfection risk associated with the Omicron variant and its

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sublineages compared to earlier SARS-CoV-2 variants.⁹ Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see [Section 3](#) below).

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

2.2. Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1. Novavax COVID-19 Vaccine

The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the [FDA website](#).

2.2.2. Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: three-dose primary series for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, and a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 5 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series and booster doses is specified for the age group in which the vaccine is being administered: 3 µg in 0.2 mL (primary series only) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 11 years of age, and 30 µg in 0.3 mL for 12 years of age and older. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are detailed in the decision memoranda available on the [FDA website](#).

2.2.3. Spikevax and Moderna COVID-19 Vaccine

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains nucleoside-modified mRNA that encodes for the full-length spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a: 2-dose primary series for individuals 6 months of age and older, and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine,

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Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 6 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years old and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is 50 µg in 0.5 mL for use in individuals 12 years of age and older . and 25 µg in 0.25 mL for use in individuals 6-11 years of age. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are detailed in the decision memoranda available on the [FDA website](#).

2.2.4. Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). The safety and effectiveness data supporting authorization for the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the [FDA website](#).

2.2.5. Therapies for COVID-19

The antiviral Veklury (remdesivir) is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19.

The immune modulator Olumiant (baricitinib) is approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

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

Antivirals: Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Molnupiravir is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom

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alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies: Bebtelovimab is authorized under EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kg with positive results of direct SARS-CoV-2 testing, who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Tixagevimab co-packaged with cilgavimab is authorized under EUA as pre-exposure prophylaxis for prevention of COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg).

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

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

3. Rationale for Booster Doses for COVID-19 Vaccines

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

While the currently authorized and approved monovalent COVID-19 vaccines in the US are based on the original SARS-CoV-2 strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available monovalent vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.^{10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20}

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.^{6, 7, 8} Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,^{1, 6, 7, 8} observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization^{1, 9, 11, 12} and lower effectiveness among the immunocompromised individuals.¹³ In Israeli experience with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older, a second booster dose improved VE overall (including a reduction in mortality), although effectiveness against mild disease decreased during a 10-week follow-up period.^{14, 16}

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3.2. June 28th VRBPAC and Subsequent Regulatory Discussions

On June 28, 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see the [FDA website](#) for background materials). The committee heard presentations on the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants in the United States and COVID-19 vaccine effectiveness (CDC) and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition were also presented (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the US. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

Following the VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and to discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see the [ICMR website](#) for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as it is currently unknown which strains will be circulating in the future.

On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent booster vaccine (Original and Omicron BA.4/BA.5) to improve protection during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent (Original and Omicron BA.4/BA.5) vaccine in relevant populations. FDA recognized that data in trial participants who would receive the bivalent (Original and Omicron BA.4/BA.5) vaccine would potentially not be available prior to the optimal timeframe for deployment of the vaccine in a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered that it may be appropriate to issue an EUA of a bivalent (Original and Omicron BA.4/BA.5) vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine (Original and Omicron BA.1), plus supportive pre-clinical animal data for the recommended bivalent vaccine (Original and Omicron BA.4/BA.5), as well as data from use of already-authorized vaccines.

3.3. Rationale for Authorization of Novavax COVID-19 Vaccine, Adjuvanted as a Booster Dose

Recently authorized bivalent COVID-19 vaccines for administration as a booster dose include an mRNA component of the original SARS-CoV-2 to provide an immune response that is broadly protective against COVID-19 and an mRNA component in common between the

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Omicron variant BA.4 and BA.5 lineages to provide better protection against COVID-19 caused by the Omicron variant. With these authorizations, the FDA also revised the scope of authorization for the monovalent mRNA COVID-19 vaccines to remove their use as booster doses.

To address the subset of the US population 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and 18 years of age and older who would elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine, the monovalent Novavax COVID-19 Vaccine, Adjuvanted provides an available alternative. The authorizations of the bivalent mRNA COVID-19 vaccines were considered for the express purpose of improving protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to each of the respective monovalent mRNA COVID-19 vaccines. However, authorization of the Novavax COVID-19 Vaccine, Adjuvanted, a vaccine based on a non-mRNA platform, for use as a first booster dose, is justified by the available safety and immunogenicity data on use of the Novavax COVID-19 Vaccine, Adjuvanted as a booster dose and the potential of Novavax COVID-19 Vaccine, Adjuvanted to restore waning VE, including against severe disease and hospitalization associated with Omicron, in a specific subpopulation of individuals who would otherwise not receive a first booster dose of a COVID-19 vaccine.

4. Regulatory Considerations for a Booster EUA

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

Based on the declaration by the Secretary of the US Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (Section 564 of the FD&C Act (21 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

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potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

4.2. FDA Guidance for Industry Related to COVID-19 Vaccines

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published the guidance for industry entitled [Development and Licensure of Vaccines to Prevent COVID-19](#) (June 2020) describing FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19.²¹ This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines. The guidance notes that the efficacy of COVID-19 vaccines should be demonstrated in adequate and well controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. The guidance notes further that safety evaluations including the size of the database required to support licensure should be no different than for other preventive vaccines for infectious diseases. Of note, this guidance does not address immunogenicity studies to infer effectiveness of booster doses for COVID-19 vaccines. However, the guidance for industry document [Emergency Use Authorization for Vaccines to Prevent COVID-19](#) (March 2022, May 2021, February 2021, originally issued October 2020) describes data needed to support the effectiveness of a modified COVID-19 vaccine against variants of concern (VOCs).²² FDA has applied these concepts to effectiveness evaluations of booster doses afforded by the prototype vaccine (refer to [Section 6](#) below).

5. EUA Amendment Request for the Monovalent Prototype Novavax COVID-19 Vaccine Booster Dose For Individuals 18 Years and Older

5.1. Summary of the EUA Request

On August 12, 2022, Novavax submitted a request to amend the EUA to include use of the Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373) for use in individuals 18 years of age and older as a booster dose after completion of primary vaccination.

The EUA amendment request included data from the booster portion of Study 301, an ongoing Phase 3 safety, efficacy, and immunogenicity study in which participants ≥ 18 years of age were offered a first booster dose of NVX-CoV2373 at least 6 months after receipt of the 2-dose primary series in the Adult Main portion of the study. The median interval between the primary series and booster dose was 10.4 months (7-13 months). The following data were provided for a subset of 298 participants who received a booster dose of NVX-CoV2373 in this portion of the study:

- Immunobridging analyses: 50% neutralizing antibody GMTs and SCRs against the reference SARS-CoV-2 strain (recombinant USA-WA1/2020) elicited at 28 days after the booster dose compared to those elicited at 14 days post-primary series, among booster dose recipients in Study 301 without evidence of prior SARS-CoV-2 infection
- Exploratory analyses: 50% neutralizing antibody titers against currently circulating variants
- Safety analyses: Solicited adverse reaction, unsolicited AE, SAE, and AESI data were provided through an extraction date of May 19, 2022 (including data that were fully cleaned through March 15, 2022)

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Additionally, following an FDA request for additional available SAE and AESI safety data, the Sponsor provided data from 12,738 participants who were enrolled in Study 301 as of March 26, 2022, and received a NVX-CoV2373 booster dose following completion of a primary series. The median duration of safety follow-up for these participants was 121 days, and safety data were provided through an extraction date of August 18, 2022.

6. FDA Review of Clinical Safety and Effectiveness Data

6.1. Design

Study 2019nCoV-301 (referred to as Study 301) is an ongoing randomized, observer-blind, placebo-controlled Phase 3 study to evaluate the efficacy, safety, and immunogenicity of NVX-CoV2373 in adults ≥ 18 years of age. In the Adult Main Study portion of Study 301, participants were initially enrolled and randomized to a primary series of NVX-CoV2373 or placebo. During the course of the study, COVID-19 vaccines authorized for emergency use became available, and participants (when eligible for vaccination per national and local public health prioritization recommendations) were offered the opportunity to cross over from the originally assigned study treatment to the other study treatment (vaccine or placebo) in a blinded fashion (“blinded crossover”). After the blinded crossover period, participants ≥ 18 years of age at screening were offered the option to participate in the booster portion of the study and receive a first open-label booster dose at least 6 months after the second dose of the primary series. The open-label booster vaccination period of the Adult Main study began December 13, 2021. Through March 26, 2022, a total of 12,738 participants received a booster dose at least 6 months after completion of a 2-dose primary series of NVX-CoV2373. The booster vaccination period was initiated on December 13, 2021, and completed enrollment on May 12, 2022. At the time of the May 19, 2022, data extraction, the Omicron variant BA.2.12.1 was the predominant VOC circulating in the US.

This memo presents the study design, safety, and immunogenicity analyses pertaining to the NVX-CoV2373 booster dose only. Please see the decision memoranda available on the [FDA website](#) for information on the authorization of a 2-dose primary series of Novavax COVID-19 Vaccine, Adjuvanted.

6.1.1. Immunogenicity Evaluation

Blood samples for immunogenicity assessments were collected at 14 days after completion of a 2-dose primary series and 28 days after the booster dose of NVX-CoV2373. Prior to the administration of a booster dose, a nasal swab and blood sample were obtained to determine the study participants’ current serologic and virologic status.

Vaccine effectiveness of the NVX-Cov2373 booster dose was inferred based on an evaluation of 50% neutralizing antibody GMTs and SCRs against the reference SARS-CoV-2 strain (recombinant USA-WA1/2020) elicited at 28 days after the booster dose among booster dose recipients without evidence of prior SARS-CoV-2 infection (did not have a positive polymerase chain reaction [PCR] or anti-nucleocapsid protein [NP] swab at the time of the booster dose through Day 28 post-booster) compared to GMTs and SCRs elicited at 14 days post-primary series. Immunobridging analyses with hypothesis testing included:

- GMTs of SARS-CoV-2 neutralizing antibodies at 28 days after the booster dose versus 14 days after the second dose of the primary series, using a 0.67 non-inferiority margin, i.e., the

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lower bound of the 95% confidence interval around the ratio of GMTs needs to be >0.67 . Additionally, the point estimate of the ratio of GMTs should be >0.83 .

- Percentage of participants with seroconversion (≥ 4 -fold rise from baseline) at 28 days after the booster dose vs. 14 days after completing a NVX-CoV2373 primary series, using a -10% non-inferiority margin as the success criterion for the lower bound of the 95% confidence interval around the difference between SCRs.

The difference in the immunogenicity sampling time point following the primary series (14 days) and booster dose (28 days) is noted. The impact of any potential difference in antibody kinetics at these time points on the immunogenicity analyses is unknown, although data from early phase studies suggested peak antibody responses were observed at 14 days after the primary series.

Exploratory analyses in a limited number of participants included assessments of post-primary series and post-booster dose neutralizing antibody titers: (1) against the Omicron BA.1 sublineage using a validated MN_{50} assay and (2) against ancestral SARS-CoV-2 (Wuhan-like strain), Delta strain, Omicron BA.1 variant, and Omicron BA.5 variant (B.1.1.529) using a validated (non-validated for BA.5) pseudotype virus neutralization assay.

6.1.2. Safety Evaluation

Safety assessments following a NVX-CoV2373 booster dose include the following:

- Participants observed for at least 30 minutes post-vaccination for any immediate reaction.
- Solicited local (pain, tenderness, erythema, and swelling/induration) and systemic (fever, malaise, fatigue, arthralgia, myalgia, headache, nausea/vomiting) ARs during the 7 days following vaccination (also described as reactogenicity symptoms).
- Unsolicited AEs and MAAEs through 28 days post booster dose; and
- MAAEs attributed to study vaccine, SAEs, and AESIs (defined as COVID-related AEs and PIMMCs; see [Appendix A](#)) for the 2-year duration of the study.

6.2. Demographics and Disposition

Analysis populations included the following:

- Booster Analysis Set (n=298): a subset of participants 18 years of age and older selected from 7 US sites using the following criteria:
 - Cohort 1: participants originally randomized to placebo who received a primary series of NVX-CoV2373 following blinded crossover, received a NVX-CoV2373 booster dose, completed the blood sample collection visit post-booster dose, and did not have a positive PCR or anti-NP swab on or before the booster dose.
 - Cohort 2: participants originally randomized to a primary series of NVX-CoV2373 in the pre-crossover portion of the study, then two doses of placebo after crossover; received a NVX-CoV2373 booster dose on or before February 11, 2022, completed the blood sample collection visit post-booster dose, and did not have a positive PCR or anti-NP swab on or before the booster dose.
- Booster Per-Protocol Immunogenicity (PP-IMM) analysis set for neutralizing antibody against SARS-CoV-2 wild-type virus (n=243): a subset of participants in the Booster Analysis Set who had at least a baseline and 1 serum neutralizing antibody result available after vaccination, had no major protocol violations that were considered clinically relevant to impact immunological measures at the visit in question, and were PCR negative or anti-NP antibody negative from the time of the NVX-CoV2373 booster dose through Day 28 post-

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booster. Immunobridging analyses were based on participants in the PP-IMM who had results for both primary series and booster timepoints (n=239).

- Total Booster Set (n=12,738): All participants who completed a primary series and received a booster dose through the data cut-off of March 26, 2022.

The disposition of the Booster Analysis Set is described in [Table 1](#).

Table 1. Disposition of Booster Analysis Set

Parameter	Booster Analysis Set N=298
Booster Analysis Set	298
PP-IMM Analysis Set for neutralizing antibody against SARS-CoV-2 wild-type virus	243
Participants with at least 1 protocol deviation ¹ , n (%)	25 (8.4)
Deviations leading to exclusion from PP-IMM analysis set, n (%)	--
Visit schedule	4 (1.3)
Visit outside protocol window	4 (1.3)
Concomitant medications	1 (0.3)
Took prohibited medication during treatment	1 (0.3)
PP-IMM Analysis Set with MN titers at both post-primary series and post-booster timepoints	239

Source: EUA 28237 amendment 91 q1 tables.pdf, adapted from Tables 8 and 9.

Abbreviations: PP-IMM=Per-Protocol Immunogenicity; MN=microneutralization

1. Some participants reported more than 1 protocol deviation.

Demographic and baseline characteristics for participants in the Booster and PP-IMM analysis sets are summarized in [Table 2](#). The median age of participants in the Booster and PP-IMM analysis sets was 50 and 52 years of age, respectively. Booster dose recipients were predominantly White, and approximately 55% had comorbidities that constituted risk factors for severe COVID-19 (e.g., obesity, chronic lung disease, diabetes mellitus type 2, chronic kidney disease). No participants in the Booster and PP-IMM analysis sets subsets had cardiovascular disease or HIV. The Booster and PP-IMM analysis sets contained fewer Black and Hispanic participants compared with the Total Booster Set (see [Table 3](#)).

Table 2. Demographics and Baseline Characteristics

Characteristic	Booster Analysis Set N=298	PP-IMM N=243
Sex, n (%)	--	--
Male	156 (52.3)	124 (51.0)
Female	142 (47.7)	119 (49.0)
Age at time of booster (years)	--	--
Mean (SD)	48.1 (14.17)	49.1 (14.25)
Median	50.0	52.0
Minimum, maximum	19, 79	19, 79
Age group, n (%)	--	--
18-64 years	263 (88.3)	212 (87.2)
≥65 years	35 (11.7)	31 (12.8)

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Characteristic	Booster Analysis Set N=298	PP-IMM N=243
Race, n (%)	--	--
White	246 (82.6)	198 (81.5)
Black or African American	29 (9.7)	27 (11.1)
American Indian or Alaska Native	1 (0.3)	1 (0.4)
Native Hawaiian or Other Pacific Islander	1 (0.3)	1 (0.4)
Asian	16 (5.4)	12 (4.9)
Mixed origin (multiple)	5 (1.7)	4 (1.6)
Ethnicity, n (%)	--	--
Hispanic or Latino	48 (16.1)	38 (15.6)
Not Hispanic or Latino	250 (83.9)	205 (84.4)
High-risk adults, ¹ n (%)	--	--
Yes	281 (94.3)	227 (93.4)
No	17 (5.7)	16 (6.6)
Comorbidities (yes)	--	--
Obesity (BMI >30 kg/m ²)	108 (36.2)	85 (35.0)
Chronic kidney disease	3 (1.0)	3 (1.2)
Chronic lung disease	51 (17.1)	40 (16.5)
Cardiovascular disease	0	0
Diabetes mellitus type 2	30 (10.1)	23 (9.5)

Source: Booster analysis set: FDA-generated from dataset. PP-IMM: EUA 28237 amendment 91 q1 tables.pdf, Table 6.

Abbreviations: BMI=body mass index; PP-IMM=Per-Protocol Immunogenicity; SD=standard deviation.

PP-IMM analysis Set: Participants who had at least a baseline and 1 neutralizing antibody result available after booster vaccination and had no major protocol violations that were considered clinically relevant to impact immunological measures at the visit in question.

1. High-risk adults are defined as (1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances and (2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

Demographics and disposition of the Total Booster Set

As of March 26, 2022, 12,738 participants had received a NVX-CoV2373 booster dose following completion of a primary series, comprising the Total Booster Set.

Table 3. Demographics and Baseline Characteristics, Total Booster Population

Characteristic	Total Booster Set (N=12,738)
Sex, n (%)	--
Male	6449 (50.6)
Female	6289 (49.4)
Age group, n (%)	--
18 to 64 years	10732 (84.3)
≥65 years	2006 (15.7)
Age (years)	--
Mean (SD)	48.9 (14.74)
Median	50.0
Minimum - maximum	18 - 96

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Characteristic	Total Booster Set (N=12,738)
Race, n (%)	--
White	9249 (72.6)
Black or African American	1835 (14.4)
American Indian or Alaska Native	830 (6.5)
Native Hawaiian or other Pacific Islander	28 (0.2)
Asian	490 (3.8)
Mixed origin	220 (1.7)
Not reported	82 (0.6)
Missing	4 (<0.1)
Ethnicity, n (%)	--
Hispanic or Latino	2729 (21.4)
Not Hispanic or Latino	9973 (78.3)
Not reported	21 (0.2)
Unknown	14 (0.1)
Missing	1 (<0.1)
Country, n(%)	--
Mexico	656 (5.1)
United States	12082 (94.9)
High risk adults, n (%)	--
Yes	12212 (95.9)
No	526 (4.1)
Co-morbidities, (yes)	--
Obesity (BMI >30 kg/m ²)	5427 (42.6)
Chronic kidney disease	124 (1.0)
Chronic lung disease	1973 (15.5)
Cardiovascular disease	171 (1.3)
Diabetes mellitus Type 2	1286 (10.1)

Source: EUA 28237 amendment 96, booster analysis set: FDA-generated from dataset, all serostatus table.

Abbreviations: BMI=body mass index; SD=standard deviation.

Notes: For booster period, treatment group reflects treatment received in the initial period. Cohort 1 includes subjects who received placebo during the initial period and were planned to receive SARS-CoV-2 in the blinded crossover period. Cohort 2 includes subjects who received SARS-CoV-2 in the initial period. Percentages are calculated based on subjects in booster analysis set in each column (N). Age for booster period is calculated as (date of birth date -booster date +1)/365.25.

n for continuous parameters represents the number of subjects with non-missing values for that parameter.

6.3. Timing of NVX-CoV2373 Booster Administration

Booster doses were administered at least 6 months after the primary series. The median interval between completion of the NVX-CoV2373 primary series and the booster dose was 10 months (range 7 to 13 months) for the Booster Analysis Set and of 11 months (range 6 to 14 months) for the Total Booster Set.

6.4. Immunogenicity Evaluation

6.4.1. Primary immunogenicity analyses

Of the 243 participants included in the PP-IMM, 239 had immunogenicity data available for both primary series and booster and were included in primary immunogenicity analyses.

GMTs of neutralizing antibody titers to the reference strain

Noninferiority was assessed based on the GMT of SARS-CoV-2 neutralizing titers 28 days after the booster dose compared to 14 days after completion of a primary series. The ratio of GMT at

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28 days after the booster dose to the GMT at 14 days after completion of a primary vaccination series and the corresponding 95% CI were estimated from a paired t-test. The per-protocol prespecified statistical success criteria for demonstrating non-inferiority required the point estimate of the GMR being >0.83 and the lower limit of the 95% CI around the GMR being >0.67.

The 50% neutralizing GMTs at 28 days post-booster dose were 3.4-fold higher than those observed at 14 days post-primary series, which met the immunobridging success criteria for GMTs against the reference strain, as shown in [Table 4](#) below.

Table 4. Ratio of Neutralizing Antibody Titers (MN₅₀) Against SARS-CoV-2 Wild-Type Virus 28 Days After the Booster Dose of NVX-CoV2373 Versus 14 Days After the Second Dose of NVX-CoV2373 (Primary Series) in the Adult Main Study of Study 301, PP-IMM Analysis Set¹

Post-Booster GMT N=239 (95% CI) ²	Post-Primary Series GMT N=239 (95% CI) ²	GMR (Booster/Primary Series) (95% CI) ²	Met Success Criteria LB of 95% CI >0.67 Point estimate >0.83
5075.6 (4448.3, 5791.4)	1505.7 (1244.1, 1822.3)	3.4 (2.8, 4.0)	Yes

Source: EUA 28237 amendment 91 q1 tables.pdf, adapted from Table 10.

Assay: Microneutralization assay using ancestral SARS-CoV-2 (Wuhan-like strain)

Abbreviations: CI=confidence interval; GMR=geometric mean fold rise; GMT=geometric mean titer; LB=lower bound;

MN₅₀=microneutralization assay with an inhibitory concentration of 50%; N=number of participants with non-missing neutralizing antibody titer results at the visit; PP-IMM=Per-Protocol Immunogenicity analysis set

1. The analysis included a total of 239 participants of the PP-IMM analysis set who had immunogenicity data available for both the booster and primary series.

2. The 95% CI for GMT and GMR were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.

Rates of neutralizing antibody seroconversion to the reference strain

Noninferiority was assessed based on the difference between the percentage of participants achieving seroconversion following the booster dose (defined as a ≥4-fold rise at 28 days after booster dose from pre-booster) and following the primary series (defined as ≥4-fold rise at 14 days after the primary series compared to pre-Dose 1). Noninferiority was demonstrated if the lower limit of the 95% CI for the difference in percentages of participants with seroconversion (28 days post-booster minus 14 days post-primary series) was greater than -10%.

The SCR from pre-booster dose to 28 days post-booster dose (85.4%) was lower than the SCR from pre-Dose 1 to 14 days post-primary series (94.6%), reflecting that a ≥4-fold increase in titer is more difficult to achieve from a booster dose administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination. As shown in [Table 5](#), the difference in SCRs was -9.2% (95% CI: -14.4%, -4.5%), which did not meet the immunobridging success criterion for SCRs against the reference strain.

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Table 5. Seroconversion Rates for Neutralizing Antibody Titers (MN₅₀) Against SARS-CoV-2 Wild-Type Virus 28 Days After NVX-CoV2373 Booster Dose Relative to the Time of Booster Vaccination Versus 14 Days After the Second Primary Dose of NVX-CoV2373 Relative to the Time of First Vaccination in the Adult Main Study, PP-IMM Analysis Set

Booster SCR N=239 n (%) (95% CI)¹	Primary Series SCR N=239 n (%) (95% CI)¹	Booster-Primary Difference in SCR (95% CI)²	Met Success Criteria LB of 95% CI >-10%
204 (85.4) (80.2, 89.6)	226 (94.6) (90.9, 97.1)	-9.2% (-14.4%, -4.5%)	No

Source: EUA 28237 amendment 91 q1 tables.pdf, Table 11.

Assay: Microneutralization assay using ancestral SARS-CoV-2 (Wuhan-like strain)

n=number of participants with seroconversion. N=number of participants with non-missing neutralizing antibody titer results at both visits.

Abbreviations: CI=confidence interval; LB=lower bound; MN₅₀=microneutralization assay with an inhibitory concentration of 50%; PP-IMM=Per-Protocol Immunogenicity analysis set; SCR=seroconversion rate.

1. Based on Clopper-Pearson.

2. Tango method.

An additional descriptive post hoc analysis evaluated SCRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. As shown in [Table 6](#), the booster dose SCR, with seroconversion defined as at least a 4-fold rise relative to the time of first dose, was 98.3%. The difference in SCRs in this post-hoc analysis was 3.8% (95% CI 2.0%, 7.0%).

Table 6. Analysis of Seroconversion Rates Against a SARS-CoV-2 Wild-Type Virus (SARS-CoV-2 hCoV-19/Australia/VIC01/2020a) at 28 Days After a Booster Dose Versus 14 Days After Completion of the Primary Series, Participants ≥ 18 Years of Age, PP-IMM Analysis Set¹

Booster Dose SCR N=239² n (%) (95% CI)³	Primary Series SCR N=239 n (%) (95% CI)³	Difference in SCR⁴ (Booster-Primary Series) (95% CI)⁵
235 (98.3) (95.8, 99.5)	226 (94.6) (90.9, 97.1)	3.8% (2.0%, 7.0%)

Source: EUA 28237 amendment 91 adapted from Table 12.

Abbreviations: CI=confidence interval; PP-IMM=Per-Protocol Immunogenicity; SCR = seroconversion rate.

1 PP-IMM Analysis Set included all participants who received two doses (0.5 mL 3 weeks apart) of the Novavax COVID-19 Vaccine, Adjuvanted in the initial vaccination period or in the blinded crossover vaccination period, had an immunogenicity blood sample collected at Day 35, did not have serologic or virologic evidence (if available) of SARS-CoV-2 infection on or before the booster dose, did not receive an emergency use authorized COVID-19 vaccine, received the booster dose, and remained blinded on study and without major protocol deviations until 7 days post-crossover Dose 2.

2. The analysis included a total of 239 participants of the PP-IMM analysis set who had immunogenicity data (microneutralization) available for both the booster and primary series

3. 95% CI is based on the Clopper-Pearson method.

4. Based on the Tango method.

5. Booster SCR was defined as the proportion of participants with post-vaccination titers (measured 28 day post-booster) ≥4-fold higher than pre-booster titers. Primary SCR was defined as the proportion of participants with post-vaccination titers (measured 14 days after completion of 2-dose primary series) ≥4-fold higher than pre-dose 1.

Note: The median duration between the time of the second dose of the Novavax COVID-19 Vaccine, Adjuvanted and the time of the booster dose was 10 months.

Subgroup analyses of neutralizing antibody responses against SARS-CoV-2 wild-type virus

After the booster dose, neutralizing GMTs were similar among males and females, and higher among Hispanic or Latino participants (GMT 6,292) compared to non-Hispanic or Latino participants (GMT 4,880). The number of Black or African American and Asian participants was too small to draw meaningful conclusions about differences in MN response by race.

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Neutralizing GMTs and SCRs among those with comorbidities were comparable to those without comorbidities, as shown in [Table 7](#). Obesity (~76%) was the most common comorbid condition, followed by chronic lung disease (~36%) and diabetes mellitus (~20%).

Table 7. Neutralizing Antibody GMTs Against a SARS-CoV-2 Wild-Type Virus 28 Days After a Booster Dose Versus 14 Days After Completion of the Primary Series, Participants ≥18 Years of Age, PP-IMM Analysis Set

Subgroup	n ¹	Post-Booster GMT (95% CI)	n ¹	Primary Series GMT (95% CI)	N ²	Booster SCR (95% CI)	N ²	Primary Series SCR (95% CI)
With any comorbidities ³	110	4868.3 (3904.2, 6070.5)	110	1264.0 (920.2, 1736.1)	94	85.5 (77.5, 91.5)	102	92.7 (86.2, 96.8)
Without comorbidities ³	129	5259.4 (4488.1, 6163.4)	129	1748.1 (1391.1, 2196.6)	110	85.3 (78.0, 90.9)	124	96.1 (91.2, 98.7)

Source: EUA 28237 amendment 91, Response to IR 80.pdf, adapted from Table 1, page 3.

Assay: Microneutralization assay using ancestral SARS-CoV-2 (Wuhan-I ke strain)

Abbreviations: CI=confidence interval; GMT=geometric mean titer; PP-IMM=Per-Protocol Immunogenicity analysis set; SCR=seroconversion rate

1. n=Number of Study 301 participants with valid and determinate assay results for the specified assay at all 4 sampling time points.

2. N=Number participants who seroconverted. Seroconversion rate (SCR) was defined as the proportion of participants with post-vaccination levels ≥4-fold higher than the baseline levels (i.e., SCR at 28 days post-booster dose relative to time of booster dose [pre-booster] and SCR at 14 days after second dose of NVX-CoV2373 relative to time of first dose of NVX-CoV2373 [pre-Dose 1]).

3. Comorbidities include, in descending order of frequency, obesity, chronic lung disease, diabetes mellitus type 2, and chronic kidney disease.

6.4.2. Exploratory immunogenicity analyses against the Omicron Variant

Exploratory immunogenicity analyses were performed on a subset of 40 booster dose recipients, 18 of whom had both post-primary and post-booster dose data available for comparison. [Table 8](#) presents a comparison of the neutralizing (MN₅₀) GMT against the Omicron BA.1 sublineage of SARS-CoV-2 post-primary series to post-booster dose. [Table 9](#) presents the difference in SCRs for the Omicron BA.1 sublineage (post-booster compared to post-primary). A validated assay was used to measure SARS-CoV-2 Omicron BA.1 microneutralization titers.

Table 8. Ratio of Neutralizing Antibody Titers (MN₅₀) Against the Omicron BA.1 Sublineage of SARS-CoV-2 28 Days After the Booster Dose of NVX-CoV2373 Versus 14 Days After the Second Dose of NVX-CoV2373 (Primary Series)

Post-Booster GMT N=18 (95% CI) ¹	Post-Primary Series GMT N=18 (95% CI) ¹	GMFR (Booster/Primary Series) (95% CI) ¹
235.2 (150.6, 367.3)	13.6 (10.1, 18.3)	17.3 (10.6, 28.1)

Source: EUA 28237 amendment 91 q1 tables.pdf, adapted from Table 14.

SARS-CoV-2 Omicron BA.1 microneutralization assay

N=number of Cohort 2 participants with non-missing neutralizing antibody titer results at the visit. Cohort 2: initially randomized to NVX-CoV2373 group (primary series), then received NVX-CoV2373 booster dose a median of 11 months later

Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; MN₅₀=microneutralization assay with an inhibitory concentration of 50%;

1. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.

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Table 9. Seroconversion Rates for Neutralizing Antibody Titers (MN₅₀) Against the Omicron BA.1 Sublineage of SARS-CoV-2 28 Days After the Booster Dose of NVX-CoV2373 Versus 14 Days After the Second Dose of NVX-CoV2373 (Primary Series)

Booster SCR N=18 n (%) (95% CI)¹	Primary Series SCR N=18 n (%) (95% CI)¹	Booster-Primary Difference in SCR (95% CI)²
14 (77.8) (52.4, 93.6)	2 (11.1) (1.4, 34.7)	66.7 (37.4, 83.7)

Source: EUA 28237 amendment 91 q1 tables.pdf, adapted from Table 15.

SARS-CoV-2 Omicron BA.1 microneutralization assay

N=number of Cohort 2 participants with non-missing neutralizing antibody titer results at the visit. Cohort 2: initially randomized to NVX-CoV2373 group (primary series), then received NVX-CoV2373 booster dose a median of 11 months later

Abbreviations: CI=confidence interval; LB=lower bound; MN₅₀=microneutralization assay with an inhibitory concentration of 50%; SCR=seroconversion rate.

1. Based on Clopper-Pearson.

2. Tango method.

An additional exploratory immunogenicity analysis assessed neutralizing (MN₅₀) antibody GMTs against the Wuhan-Hu-1, Delta (B.1.617.2), Omicron BA.1 (B.1.351), and Omicron BA.5 (B.1.351) variants/sublineages of SARS-CoV-2 using assay that was validated for Wuhan-Hu-1, Delta, and Omicron BA.1, but non-validated for BA.5 (presented in [Table 10](#)). The primary data were not provided to FDA for independent analyses, and interpretation of the data is limited by the small number of participants.

Although an 11-fold increase was observed when comparing post-booster dose GMTs against Omicron BA.5 to post-primary series values, it is noted that GMTs against Wuhan-Hu-1 decreased post-booster dose compared to post-primary series. The significance of this finding in the context of a very limited number of participants is unclear.

Table 10. Neutralizing Antibody Titers Against Wuhan-Hu-1, Delta, Omicron BA.1, and BA.5 After 28 Days After the Booster Dose of NVX-CoV2373 Versus 14 Days After the Second Dose of NVX-CoV2373 (Primary Series)

SARS-CoV-2 Variant	Post-Primary Series GMT (95% CI) N=17	Post-Booster GMT (95% CI) N=18	GMFR (Booster/Primary Series)
Wuhan-Hu-1	7177 (3679, 13999)	3838 (2558, 5761)	0.6
Delta	4487 (2016, 9987)	8275 (5401, 12680)	1.9
Omicron BA.1	60 (35, 102)	1238 (760, 2017)	22.5
Omicron BA.5	158 (87, 285)	1571 (995, 2481)	10.9

Source: EUA 28237 amendment 95. Response-Request-85-batch 1.pdf, page 4.

Abbreviations: CI=Confidence Interval; GMFR=Geometric Mean Fold Rise; GMT=Geometric Mean Titer.

Assay: pseudotype virus neutralization assay using ancestral SARS-CoV-2 (Wuhan-like strain), Delta strain, Omicron BA.1 variant, and Omicron BA.5 variant (B.1.1.529)

N=Number of Study 301 participants' serum samples tested Cohort 2: initially randomized to NVX-CoV2373 group (primary series), then received NVX-CoV2373 booster dose a median of 11 months later.

6.5. Safety Evaluation

6.5.1. Overview of adverse events

The analyses presented for the Booster Analysis Set (n=298) were based on data through the May 19, 2022, extraction date. The Sponsor provided safety data through 28 days post-booster dose for the Booster Analysis Set; 99.3% of participants completed at least 1 month of follow up post-booster dose. Of the 298 participants, 238 (80%) provided data on local and systemic solicited adverse reactions (ARs) for at least 1 day of the 7-day post-booster dose collection

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period in an e-diary (solicited safety set). Overall, 81.5% of participants reported any local reaction and 80.3% reported any systemic reaction. A total of 11 participants (3.7%) reported at least 1 unsolicited AE within the 28-day post-booster dose collection period, including 3 participants (1%) who reported events considered by the study investigator to be related to study intervention. There were no events leading to withdrawal reported through 28 days after booster dose administration. No study participants in the Booster Analysis Set died.

At FDA’s request, the Sponsor provided additional safety data (SAEs and AESIs) for 12,738 participants (Total Booster Set) who received a NVX-CoV2373 booster dose following completion of a primary series, through a data extraction date of August 18, 2022. The median duration of safety follow-up for these participants was 121 days (range 1-241 days). Of the Total Booster Set, 173 participants reported SAEs (1.4%).

6.5.2. Immediate AEs

The Sponsor did not categorize AEs as immediate adverse events. No hypersensitivity events were reported immediately after vaccination.

6.5.3. Solicited adverse reactions

The frequencies of local and systemic solicited adverse reactions occurring within 7 days of booster are summarized in aggregate in [Table 11](#) and by age in [Table 12](#) (18-64 years old) and [Table 13](#) (≥65 years old). Injection site pain (81.1% of participants) was the most frequently reported solicited adverse reaction, following by fatigue/malaise (63.4% of participants) and headache (52.9% of participants).

Table 11. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days After NVX-CoV2373 Booster Dose, Solicited Safety Set¹

Reaction	Solicited Safety Set ¹ N=238 n (%)
Any solicited reaction, n (%)	--
Any grade	212 (89.1)
Grade 3	50 (21.0)
Grade 4	2 (0.8)
Injection site reaction, n (%)	--
Any grade ²	194 (81.5)
Grade 3	20 (8.4)
Pain/Tenderness, n (%)	--
Any grade ²	193 (81.1)
Grade 3 ³⁻⁵	18 (7.6)
Redness, n (%)	--
Any grade ²	15 (6.3)
Grade 3 ⁶	1 (0.4)
Swelling, n (%)	--
Any grade ²	20 (8.4)
Grade 3 ⁷	2 (0.8)
Systemic reaction, n (%)	--
Any grade	191 (80.3)
Grade 3 ⁸	45 (18.9)
Grade 4 ⁹	2 (0.8)

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Reaction	Solicited Safety Set¹ N=238 n (%)
Fever, n (%)	--
Any grade ²	15 (6.3)
Grade 3 ¹⁰	2 (0.8)
Fatigue/Malaise, n (%)	--
Any grade	151 (63.4)
Grade 3 ⁸	41 (17.2)
Grade 4 ⁹	2 (0.8)
Muscle pain, n (%)	--
Any grade	150 (63.0)
Grade 3 ⁸	20 (8.4)
Grade 4 ⁹	2/238 (0.8)
Joint pain, n (%)	--
Any grade ²	72 (30.3)
Grade 3 ⁸	9 (3.8)
Nausea/vomiting, n (%)	--
Any grade	35 (14.7)
Grade 3 ¹¹	2 (0.8)
Grade 4 ¹²	1 (0.4)
Headache, n (%)	--
Any grade ²	126 (52.9)
Grade 3 ¹³	14 (5.9)

Source: EUA 28237 amendment 90, adapted from Table 29

n=number of subjects who reported at least one adverse event

1. Solicited safety set includes participants who received at least one dose of study vaccine and completed at least 1 day of the 7 day post-booster follow up period in the eDiary. At each level of subject summarization, a subject is counted once for the most severe grade if the subject reported one or more events.

2. Absence of rows for Grade 4 adverse reactions indicates no events were reported.

3. Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

4. Grade 3 tenderness: Defined as significant discomfort at rest.

5. Grade 4 pain/ tenderness: Defined as Emergency Room (ER) visit or hospitalization.

6. Grade 3 redness (erythema): Defined as >10 cm.

7. Grade 3 swelling: Defined as >10 cm or prevents daily activity.

8. Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.

9. Grade 4 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as ER visit or hospitalization.

10. Grade 3 fever: Defined as 39.0 to 40°C

11. Grade 3 nausea or vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

12. Grade 4 nausea or vomiting: Defined as ER visit or hospitalization for hypotensive shock.

13. Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

The mean duration of injection site reaction was 3.1 days (range 1 to 7 days), 3.1 days for pain/tenderness (range 1 to 7 days), 1.8 days for redness (range 1 to 5 days), 2.3 days for swelling (range 1 to 7 days), 2.3 days for fatigue/malaise (range 1 to 7 days), and 2.2 days for headache (range 1 to 7 days), 2.1 days for myalgia (range 1 to 7 days), 1.8 days for arthralgia (range 1 to 6 days), and 1.9 days for nausea or vomiting (range 1 to 6 days).

Any severe (Grade 3 or higher) solicited AR was reported by 21.8% of participants following the booster dose; the most frequently reported severe solicited ARs included fatigue/malaise (17.2%) and muscle pain (8.4%). Grade 4 events included fatigue/malaise (n=2), muscle pain (n=2), and nausea/vomiting (n=1).

[Table 12](#) and [Table 13](#) describe the reactogenicity data post-booster dose compared to post-Dose 1 and 2 of the primary series by age group. Overall, local and systemic reactogenicity events were reported by a larger proportion of participants following a booster dose compared to both primary series doses. In general, as seen with the primary series, reactogenicity events

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were reported by a smaller proportion of participants 65 years of age and older compared to those 18-64 years of age.

Table 12. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days¹ After Each Dose in Participants 18-64 Years of Age, Solicited Safety Set², Dose 1 and Dose 2³, and Booster Dose

Local Adverse Reaction	Primary Series Dose 1 N=15884 n (%)	Primary Series Dose 2 N=15148 n (%)	Booster Dose Solicited Safety Set N=215 n (%)
Local adverse reactions	--	--	--
Pain/tenderness, n (%)	--	--	--
Any grade	9604 (60.5)	12234 (80.8)	178 (82.8)
Grade 3 ^{4,5}	174 (1.1)	951 (6.3)	16 (7.4)
Grade 4 ⁶	0	5 (0.03)	0
Redness (erythema), n (%)	--	--	--
Any grade ³	151 (1.0)	1040 (6.9)	14 (6.5)
Grade 3 ⁷	3 (0.02)	134 (0.9)	1 (0.5)
Swelling, n (%)	--	--	--
Any grade ³	137 (0.9)	943 (6.2)	17 (7.9)
Grade 3 ⁸	7 (0.04)	82 (0.5)	2 (0.9)
Systemic adverse reactions	--	--	--
Fever, n (%)	--	--	--
Any grade	56 (0.4)	941 (6.2)	12 (5.6)
Grade 3 ⁹	7 (0.04)	60 (0.4)	1 (0.5)
Grade 4 ¹⁰	4 (0.03)	2 (0.01)	0
Headache, n (%)	--	--	--
Any grade	4158 (26.2)	7128 (47.1)	118 (54.9)
Grade 3 ¹¹	132 (0.8)	492 (3.2)	12 (5.6)
Grade 4 ¹²	4 (0.03)	5 (0.03)	0
Fatigue/malaise, n (%)	--	--	--
Any grade	4892 (30.8)	8825 (58.3)	141 (65.6)
Grade 3 ¹³	249 (1.6)	1591 (10.5)	39 (18.1)
Grade 4 ¹²	8 (0.05)	7 (0.05)	2 (0.9)
Muscle pain (myalgia), n (%)	--	--	--
Any grade	3827 (24.1)	7682 (50.7)	142 (66.0)
Grade 3 ¹³	79 (0.5)	805 (5.3)	18 (8.4)
Grade 4 ¹²	2 (0.01)	5 (0.03)	2 (0.9)
Joint pain (arthralgia), n (%)	--	--	--
Any grade	1260 (7.9)	3542 (23.4)	67 (31.2)
Grade 3 ¹³	49 (0.3)	393 (2.6)	7 (3.3)
Grade 4 ¹²	1 (<0.01)	5 (0.03)	0

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	Primary Series Dose 1 N=15884 n (%)	Primary Series Dose 2 N=15148 n (%)	Booster Dose Solicited Safety Set N=215 n (%)
Local Adverse Reaction			
Nausea or vomiting, n (%)	--	--	--
Any grade	1069 (6.7)	1822 (12.0)	33 (15.3)
Grade 3 ¹⁴	18 (0.1)	26 (0.2)	1 (0.5)
Grade 4 ¹⁵	4 (0.03)	7 (0.05)	1 (0.5)

Source: EUA 28237 draft adult fact sheet, adapted from Table 1
n=number of subjects who reported at least one adverse event

- 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (eDiary).
- The analysis included a total of 238 participants who received the booster dose, of which a subset of the booster analysis set completed their eDiary.
- Absence of rows for Grade 4 adverse reactions indicates no events were reported.
- Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.
- Grade 3 tenderness: Defined as significant discomfort at rest.
- Grade 4 pain/ tenderness: Defined as Emergency Room (ER) visit or hospitalization.
- Grade 3 redness (erythema): Defined as >10 cm.
- Grade 3 swelling: Defined as >10 cm or prevents daily activity.
- Grade 3 fever: Defined as 39.0 to 40°C
- Grade 4 fever: Defined as >40°C
- Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.
- Grade 4 headache, fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as ER visit or hospitalization.
- Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.
- Grade 3 nausea or vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.
- Grade 4 nausea or vomiting: Defined as ER visit or hospitalization for hypotensive shock.

Table 13. Frequency of Solicited Local and Systemic Adverse Reactions Within 7 Days¹ After Each Dose in Participants ≥65 Years of Age, Solicited Safety Set², Dose 1, Dose 2³, and Booster Dose

Event	Primary Series Dose 1 N=2251 n (%)	Primary Series Dose 2 N=2048 n (%)	Booster Dose Solicited Safety Set N=23 n (%)
Local adverse reactions	--	--	--
Pain/tenderness, n (%)	--	--	--
Any grade ³	854 (37.9)	1258 (61.4)	15 (65.2)
Grade 3 ^{4,5}	13 (0.6)	43 (2.1)	2 (8.7)
Redness (erythema), n (%)	--	--	--
Any grade ³	16 (0.7)	99 (4.8)	1 (4.3)
Grade 3 ⁶	0	7 (0.3)	0
Swelling, n (%)	--	--	--
Any grade ³	18 (0.8)	111 (5.4)	3 (13.0)
Grade 3 ⁷	1 (0.04)	8 (0.4)	0
Systemic adverse reactions	--	--	--
Fever, n (%)	--	--	--
Any grade ³	8 (0.4)	40 (2.0)	3 (13.0)
Grade 3 ⁸	1 (0.04)	2 (0.1)	1 (4.3)
Headache, n (%)	--	--	--
Any grade	344 (15.3)	502 (24.5)	8 (34.8)
Grade 3 ⁹	12 (0.5)	18 (0.9)	2 (8.7)
Grade 4 ¹⁰	1 (0.04)	1 (0.05)	0
Fatigue/malaise, n (%)	--	--	--
Any grade ³	444 (19.7)	714 (34.9)	10 (43.5)
Grade 3 ¹¹	23 (1.0)	68 (3.3)	2 (8.7)

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Event	Primary Series Dose 1 N=2251 n (%)	Primary Series Dose 2 N=2048 n (%)	Booster Dose Solicited Safety Set N=23 n (%)
Muscle pain (myalgia), n (%)	--	--	--
Any grade ³	284 (12.6)	561 (27.4)	8 (34.8)
Grade 3 ¹¹	3 (0.1)	32 (1.6)	2 (8.7)
Joint pain (arthralgia), n (%)	--	--	--
Any grade	139 (6.2)	271 (13.2)	5 (21.7)
Grade 3 ¹¹	4 (0.2)	16 (0.8)	2 (8.7)
Grade 4 ¹⁰	0	1 (0.05)	0
Nausea/vomiting	--	--	--
Any grade ³	81 (3.6)	108 (5.3)	2 (8.7)
Grade 3 ¹²	0	3 (0.1)	1 (4.3)

Source: EUA 28237 draft adult fact sheet, adapted from Table 2

1. 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (eDiary).

2. The analysis included a total of 238 participants who received the booster dose, of which a subset of the booster safety analysis set who completed their eDiary 3. Absence of rows for Grade 4 adverse reactions indicates no events were reported.

4. Grade 3 pain: Defined as any use of narcotic pain reliever or prevents daily activity.

5. Grade 3 tenderness: Defined as significant discomfort at rest.

6. Grade 3 redness (erythema): Defined as >10 cm.

7. Grade 3 swelling: Defined as >10 cm or prevents daily activity.

8. Grade 3 fever: Defined as 39.0 to 40°C (102.1 to 104°F).

9. Grade 3 headache: Defined as significant; any use of narcotic pain reliever or prevents daily activity.

10. Grade 4 headache, joint pain (arthralgia): Defined as ER visit or hospitalization.

11. Grade 3 fatigue/malaise, muscle pain (myalgia), joint pain (arthralgia): Defined as significant; prevents daily activity.

12. Grade 3 nausea or vomiting: Defined as prevents daily activity, requires outpatient intravenous hydration.

6.5.4. Unsolicited Adverse Events

6.5.4.1. Booster Analysis Set

[Table 14](#) summarizes unsolicited treatment emergent adverse events (TEAEs) reported through 28 days after the booster dose in Booster Analysis Set. Of the 298 participants, 11 (3.7%) reported a total of 13 unsolicited TEAEs, including 2 participants who reported a total of 3 SAEs. The lack of comparator group precludes assessment for increased frequencies of specific events. No new signals emerged from review of the reported events.

Table 14. Summary of Unsolicited Adverse Events Through 28 Days After the Third (Booster) Dose of NVX-CoV2373 in All Participants, Booster Analysis Set

TEAE Category	Booster Analysis Set N=298 n (%)
Any TEAE	11 (3.7)
Any severe TEAE	0
Any related TEAE	3 (1.0)
Any serious TEAE	2 (0.7)
Any MAAE	7 (2.3)
Any TEAE leading to study discontinuation	0
Any TEAE resulting in death	0
Any AESI	0

Source: EUA 28237 amendment 91 q1 tables.pdf, Table 33.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; n=number of participants experiencing the AE; N=number of participants in the Ad-Hoc Safety Analysis Set; PIMMC=potential immune-mediated medical condition; TEAE=treatment-emergent adverse event.

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Non-serious unsolicited TEAEs

A total of 9 participants reported 10 TEAEs of mild to moderate severity. One participant had 2 TEAEs of arthralgia (hip and elbow 12 days following booster dose), and the following TEAEs were reported in 1 participant each: lymphadenopathy, hypothyroidism, cataract, injection site pain, COVID-19 (described in [Section 6.6](#)), melanocytic nevus, neuralgia, and rhinorrhea. Three participants reported events considered related to NVX-CoV2373 booster vaccination, including lymphadenopathy (n=1), neuralgia (n=1), injection site pain (n=1), with onset 1, 4, and 7 days after vaccination, respectively. The event of neuralgia was moderate in severity and resolved after 49 days; ibuprofen was administered as needed.

No AESIs (defined in [Appendix A](#)) were reported by the 298 booster cohort participants.

SAEs through 28 days after booster dose

Data for SAEs in the Booster Analysis Set were provided by the Sponsor and are incorporated in the review of SAEs for the Total Booster Set, as described in [Section 6.5.4.2](#).

Subgroup analyses for safety

When comparing risk differences between the NVX-CoV2373 and placebo arms across the race groups, participants who are White had numerically higher rates of solicited AEs compared to Black participants. Female had numerically higher rates of solicited AEs compared to male participants. Hispanic participants had slightly higher rates of solicited reactions than non-Hispanic participants.

6.5.4.2. Total Booster Set

At FDA's request for safety data from longer term follow up in all booster dose recipients, the Sponsor provided AESI and SAE data for 12,738 participants who had completed a primary series and had received a NVX-CoV2373 booster through March 26, 2022. The data were cleaned through March 26, 2022, with an extraction date of August 18, 2022. The median safety follow-up duration was 121 days post-booster dose (range 1-241).

Withdrawal due to AE

Two participants withdrew due to AEs that were temporally distant from booster dose administration and considered by the investigator and FDA to be unrelated to the booster dose. These included a fall, spinal compression fracture, and spinal cord hematoma 98 days after booster administration and an ischemic stroke 85 days after booster administration.

AESIs

A total of 18 AESIs were reported by 14 participants (0.1%), including the following:

- Events of autoimmune hepatitis and elevated hepatic enzymes with onset 12 and 2 days following vaccination, respectively, which are considered possibly related to the booster dose vaccination by FDA and are described in additional detail below.
- An AESI of viral myocarditis associated with COVID-19 is described in additional detail in the [SAE](#) section below.
- Three events of pulmonary embolism were reported on Days 22, 148, and 149 post-booster, respectively. Events of pulmonary embolism are described in additional detail in the [SAE](#) section below.

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The remaining AESIs included:

- An event of psoriatic arthropathy was reported in a participant with pre-existing psoriasis on Day 20 post-booster dose.
- Events of chest pain and Sjogren's syndrome were reported on Days 26 and 55, respectively, in a 33-year-old female with generalized arthralgia and fatigue for approximately 10 years and brain fog and forgetfulness for approximately 5 years. The chest pain resolved spontaneously and was attributed to anxiety. The participant did not have dry eyes or dry mouth and reported that the onset of her chronic symptoms of fatigue, brain fog, and arthralgias leading to the diagnosis of Sjogren's syndrome preceded enrollment in the study and did not worsen during the course of the study.
- Three neurologic events were reported, including Bell's palsy Day 37 days post-booster, neurosensory deafness Day 72 days post-booster dose, and Guillain Barré syndrome 91 days post-booster.
- Two oncologic events were reported, including chronic lymphocytic leukemia Day 121 post-booster and malignant frontal lobe mass Day 148 post-booster.
- An event of ulcerative colitis was reported Day 61 post-booster but was later removed as an AESI because of lack of biopsy confirmation.

With the exception of the hepatic events, FDA considered the remaining AESIs unlikely to be related to vaccination, due to temporal and/or biologic implausibility and/or underlying risk factors. There was no specific pattern of events identified to suggest a new safety signal.

Hepatic AESIs

The 2 hepatic AESIs are described in additional detail as follows:

- A 57-year-old male with history of unspecified atopic disorders, gastrointestinal atonic and hypomotility disorders, and allergies to foods and drugs was diagnosed with autoimmune hepatitis approximately 12 days (exact date unknown) after booster dose vaccination and was subsequently treated with azathioprine. This event was assessed as moderate in severity. Review of liver function testing obtained in the prior year identified a history of elevated alanine aminotransferase (ALT), with maximum values 1 to 3 times the upper limit of normal (ULN). Following primary series vaccination, ALT values >4 times the ULN were observed, which subsequently decreased to 2 to 3 times the ULN. Following booster vaccine administration on January 21, 2022, the ALT increased to >7 times the ULN. The participant had a concomitant increase of aspartate aminotransferase (AST) levels but no increase in bilirubin or alkaline phosphatase. See [Table 15](#) for detailed information on hepatic test values. Autoimmune workup revealed positive antinuclear antibodies with a homogenous pattern 1:160, and actin smooth muscle antibodies 23 (normal range: 0-19, units not provided). Hepatitis serologies have been negative and per information available at this time, no alternative etiology has been identified. The outcome of illness is not recovered/not resolved at the time of the report.

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Table 15. Liver Function Tests for Participant with Autoimmune Hepatitis

Test	15Jan 2020	27May 2020	23Jun 2020	08Mar 2021	08Jun 2021	16Jul 2021	08Sep 2021	15Nov 2021	24Jan 2022	28Jan 2022
Alkaline phosphatase (RR 39-117) IU/L	98	106	106	99	108	90	87	91	88	95
Aspartate aminotransferase (RR 0-40) units/L	31	79	67	37	94	113	68	86	202	193
Alanine aminotransferase (RR 0-44) units/L	50	130	102	46	177	188	109	138	337	364
Bilirubin total (RR 0.0-1.2) mg/dL	0.4	0.7	0.6	0.3	0.4	0.7	0.6	0.4	0.6	0.9

Source: EUA 28237 amendment 93

Abbreviations: IU=international units; Jan=January; Jun=June; Jul=July; Mar=March; RR=reference range; Sep=September; Nov=November

The investigator and Sponsor assessed this AE as not related to vaccine. Due to recurrence of worsening ALT following the booster vaccination and the temporal relationship to the booster dose, FDA assesses autoimmune hepatitis as possibly related to NVX-CoV2373 booster dose vaccination; currently available information for this event is insufficient to determine a causal relationship with the vaccine. FDA assesses this autoimmune hepatitis as a serious safety concern.

Autoimmune hepatitis is a form of drug induced liver injury that has been caused by viral vaccines including influenza A, and hepatitis A and B.²³ The pattern of liver abnormalities in this participant does not meet Hy’s Law, which is the definition used by the FDA as an indicator of clinical concern for drug-induced liver injury and includes the following: ALT or AST >3x ULN, total bilirubin >2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (for example, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury).

- A 57-year-old participant had an AESI of increased hepatic enzymes (AST 38 [normal 0-40] ALT 54 [normal 0-44]) 2 days after vaccination. This event was mild in severity and with assessed as related by the investigator. There is no additional information available for this report, and the limited amount of detail precludes a full assessment of causality.

Although the currently available information for hepatic events is insufficient to determine a causal relationship with the NVX-CoV2373, further assessment of hepatic events, including autoimmune hepatitis, as a safety outcome in post-authorization surveillance safety studies is warranted.

SAEs

Of the Total Booster Set (n=12,738), 173 participants reported SAEs (1.4%).

SAEs were most frequently reported in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) *Infections and infestations* (n=52 participants; 0.4%). The most commonly reported SAEs included COVID-19 (n=10; 0.08%); sepsis (n=9; 0.07%); pneumonia (n=7; 0.05%); and acute respiratory failure, chest pain, pulmonary embolism, and anemia (n=6 each; 0.05%).

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A total of 5 participants (0.04%) reported SAEs that were considered related by the investigator, described in detail below in the [Related SAEs](#) section below.

SAEs of particular clinical interest ([myocarditis/pericarditis](#), [hypersensitivity](#), [cholecystitis](#), and [cardiac](#) events) are described in additional detail in the respective sections below.

Although there is no comparator group, precluding assessment of increased frequency of events, review of the available data for the remaining events, including narratives, did not identify any new safety concerns. In general, the SAEs appear to be consistent with expected patterns of disease in the vaccinated population.

Related SAEs

A total of 5 participants reported SAEs considered related to the NVX-CoV2373 booster dose, including acute myocardial infarction (MI) in a 28-year-old male 3 days post-booster dose, acute respiratory failure and asthma in a 59-year-old female 2 days post-booster dose, cholecystitis in a 37-year-old male 95 days post-booster, deep vein thrombosis (DVT) and pulmonary embolism in a 35-year-old female 7 days post-booster dose. These cases are described in detail in the respective sections below, including FDA's assessment of causality.

The remaining related SAE of cellulitis was reported by a 58-year-old male with history of obesity 3 days after vaccination. The participant presented with fever and erythema and purulence on the right deltoid (injection site). The subject was seen by an Infectious Disease specialist who ascribed the event to an allergic reaction that progressed to cellulitis. He was treated with 2 days of intravenous antibiotics followed by oral cephalexin for 10 days and oral prednisone for 7 days. This was assessed as related by investigator, and the verbatim term was "worsening allergic reaction to study vaccine". The event was resolved after 12 days. FDA agrees the injection site reaction is related the vaccine, although the subsequent event of cellulitis may be related to the injection procedure.

Myocarditis/Pericarditis

Clinical trial data provide evidence for increased risks of myocarditis and pericarditis following administration of a primary series of Novavax COVID-19 Vaccine, Adjuvanted. Within 10 days following vaccination, 5 cases of myocarditis and/or pericarditis were reported in participants 12 years of age or older who received Novavax COVID-19 Vaccine, Adjuvanted or a COVID-19 vaccine containing SARS-CoV-2 recombinant spike protein and Matrix-M adjuvant, manufactured by a different process. No cases of myocarditis and/or pericarditis were reported within 10 days following receipt of placebo. The cases of myocarditis and/or pericarditis were reported following vaccine Dose 1 (n=1) and Dose 2 (n=3). At the time of authorization of the primary series, one additional case in a 28-year-old male following the booster dose had been identified and was described in the [EUA Review Memorandum](#) for the primary series. An additional case of viral myocarditis was reported in the Booster Analysis Set. These 2 cases are described below:

- A 28-year-old male reported a serious event of chest pain 3 days following the booster dose. The participant had elevated troponin (~300 ng/L) and the initial differential diagnosis included myocarditis. The participant was hospitalized for 2 days and the event resolved. This event was ultimately adjudicated as a non-ST elevation myocardial infarction (NSTEMI); however, clinical features could also be consistent with myocarditis (chest pain and elevated troponin), and cardiac catheterization and cardiac magnetic resonance imaging (MRI) were not performed during the acute presentation. A cardiac MRI performed

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approximately 5 months later demonstrated left ventricular hypertrophy with minimal mitral regurgitation and normal left ventricular function with no evidence of prior myocardial infarction, myocarditis, or infiltrative cardiomyopathy. This event was assessed by the investigator and FDA as related to vaccination.

- A 60-year-old male participant with a history of hypertension reported shortness of breath, cough, abdominal pain, hypertension, and dizziness 8 days post-booster dose. He presented to the hospital with hypoxia (O₂ saturation 68%) and a troponin of 0.029 ng/mL. He was diagnosed with COVID-19 pneumonia, acute respiratory failure, myocarditis due to COVID-19, and congestive heart failure (CHF). Cardiac echocardiography on Day 10 post-booster demonstrated an ejection fraction of 25% and aneurysmal dilation of the left ventricle. Cardiac catheterization on Day 14 post-booster showed mild to moderate non-flow limiting coronary artery disease (CAD). Due to the CHF, an implantable cardioverter defibrillator participant was placed. The event is recovering/resolving. FDA assesses that concomitant COVID-19 is a plausible alternative etiology for the viral myocarditis and that the event is unlikely to be related to vaccination.

Among the 5 identified cases of myocarditis and/or pericarditis without an alternative etiology in the clinical development program, 4 occurred in males 16 through 28 years of age and 1 occurred in a female 60 years of age. Short-term follow-up data are available for 4 of these study participants, all of whom had resolution of myocarditis or pericarditis. Information is not yet available about potential long-term sequelae. As described further in [Section 7.3](#), myocarditis and/or pericarditis are considered important identified risks and ongoing pharmacovigilance activities address this risk.

Myocardial infarction and cardiac failure

A total of 23 participants reported events in the MedDRA SOC Cardiac disorders. Of these participants, 15 reported SAEs consistent with the medical concepts of myocardial infarction (MI) or cardiac failure, including the NSTEMI described above, which was the only event considered related to vaccination. The remaining cardiac SAEs included arrhythmias, mitral valve incompetence, or angina events, all of which were considered not related to vaccine.

Excluding the event of NSTEMI described above, 3 additional events of MI and 3 events of coronary artery disease are described below:

- A 29-year-old male with a history of obesity and polysubstance abuse was hospitalized for SAEs of cardiac failure, substance abuse, and acute MI (NSTEMI) 4 days after booster vaccination. The peak troponin was 4,593.8 ng/mL (normal <1 ng/mL). A cardiac echocardiogram showed mildly dilated left ventricle. A cardiac echography revealed left ventricle cavity size mildly dilated with mild hypertrophy and mildly reduced systolic function with an estimated ejection fraction of 45-50%. Cardiac catheterization 12 days after booster showed possible left circumflex artery thrombus, for which atherectomy was performed and heparin was started. These events were attributed to illicit substance use with stimulants. The subject was discharged from the hospital with an angiotensin receptor neprilysin inhibitor, and the event subsequently resolved. The study investigator considered the event not related to vaccination. FDA agrees with the investigator's assessment, as the reported illicit drugs are known to be associated with vasospasm and myocardial infarction and provide a plausible alternative etiology.
- A 56-year-old female with a history of chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, alcohol abuse, and smoking reported SAEs of NSTEMI, community acquired pneumonia, ethanol withdrawal syndrome, and acute hypoxic

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respiratory failure 52 days after the booster dose. A cardiac stent was placed and the participant was re-hospitalized 2 days later with pneumonia, sepsis without septic shock, acute on chronic congestive heart failure, COPD exacerbation, and NSTEMI. Initial troponin levels were 366 and 667 (unit and reference range (RR) were not provided). Additional events of NSTEMI were reported 72 and 138 days post-booster. Additional events of acute on chronic cardiac failure were reported 72 and 79 days post-booster. The study investigator considered the cardiac events not related to vaccination. FDA agrees with the investigator's assessment, given the temporal distance from vaccination, multiple pre-disposing risk factors, and concurrent infectious illness with the initial events of NSTEMI.

- A 64-year-old female with a history of obesity and diabetes reported an SAE of myocardial infarction 105 days after the booster dose and underwent cardiac stent placement. The study investigator considered the event of myocardial infarction not related to vaccination. FDA agrees with the investigator's assessment, given the temporal distance from vaccination and multiple pre-disposing risk factors.
- Three participants reported SAEs of coronary artery disease, including 2 with onset 114 and 119 days after the booster dose, respectively, both of which occurred in participants with risk factors for or a history of coronary artery disease. A 52-year-old female with a history of coronary artery disease, peripheral arterial disease, type 1 diabetes and tobacco use reported an SAE of worsening coronary artery disease (CAD) Day 17 post-booster dose. The case report did not include information on any symptoms or the rationale for the diagnosis of worsening disease. The participant underwent elective coronary artery bypass graft. This event was attributed to underlying diseases, including diabetes, that likely contributed to CAD. The study investigator considered the event not related to vaccination. FDA agrees with the investigator's assessment; the existing coronary and peripheral arterial disease suggest long-standing cardiovascular disease.

Three participants experienced fatal events of cardiac arrest, each of which is described in more detail in the [Deaths](#) section below.

In addition to events of cardiac failure reported in association with other cardiac events in 3 participants as described above, 2 participants reported serious events of cardiac failure.

- A 59-year-old male with a history of hypertension, type II diabetes mellitus, obesity, hypercholesterolemia, chronic kidney disease, and COPD reported an SAE of congestive heart failure 59 days after the booster dose. The estimated glomerular filtration rate was 14 (African American RR: greater than 60) and the brain natriuretic peptide value was greater than 2300 (units not provided) which was determined to be consistent with heart failure. An echocardiogram showed left ventricular hypertrophy, visually estimated ejection fraction of 55-60%, and Grade 1 diastolic dysfunction. The study investigator considered the event not related to vaccination. FDA agrees with the investigator's assessment due to lack of temporal relationship and multiple pre-disposing risk factors.
- A 64-year-old male with no significant medical history reported COVID-19 on the day of the booster dose and serious events of atrial fibrillation and new onset heart failure 146 days after the booster dose. Transthoracic echocardiogram showed an ejection fraction (EF) of 35-40%. The study investigator considered the event not related to vaccination. FDA agrees with the investigator's assessment due to lack of temporal relationship. Intercurrent COVID-19 may also have contributed to increased cardiovascular risk.

In summary, no new cardiac concerns were identified based on review of the available safety data.

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Hypersensitivity

Hypersensitivity events were evaluated using FDA-developed software to evaluate unsolicited adverse events of clinical interest using broad and narrow Standardized MedDRA Queries (SMQs) to search for preferred terms (PTs) that could together represent various medical concepts. Three PTs reported by 2 participants were identified. An evaluation of the timing of events and precipitating factors suggests alternative etiologies. One was assessed as related by the investigator, but has a plausible alternative etiology:

- A 59-year-old female with a history of asthma triggered by cold weather had SAEs of acute respiratory failure with hypoxia and asthma exacerbation 2 days after booster vaccination. These events required hospitalization, nasal canula oxygen, and treatment with inhalers and steroids. The events lasted 5 days and subsequently resolved. The investigator assessed this AE as related to vaccination. The FDA reviewer assesses the AEs as more likely related to pre-existing asthma with cold exacerbation in the month of January, although there is a temporal relationship to vaccine and it is possible that reactogenicity following the booster dose served as a potential asthma trigger.
- An SAE of anaphylaxis was reported by a 31-year-old female with history of drug hypersensitivity and allergies on Day 19 post booster that was attributed to aged cheese associated with chips she had eaten. Due to temporal implausibility and clear alternative etiology, FDA does not consider this event related to vaccination.

Biliary

Three participants had events of cholangitis and cholecystitis. Of these 3 participants, one had onset of the event within 7 days of vaccination and one was assessed as related by the investigator; these events are described in detail below. The remaining event had onset 102 days following vaccination and was considered unlikely to be related to vaccination by FDA.

- A 48-year-old female with a history of cholecystectomy and obesity reported SAEs of cholangitis and bile duct stone in a retained common bile duct stent on Day 7 post-booster dose. The investigator considered the event not related to vaccination. FDA agrees with the investigator's assessment as the bile duct stone and bile duct stent provide a plausible alternative etiology.
- A 36-year-old male with no previous medical history had cholecystitis on Day 95 after booster vaccination that was assessed as related by the investigator. The FDA assesses the event as unlikely to be related to the vaccine due to temporal implausibility.

Thromboembolic and neurovascular

A total of 9 participants reported 12 thrombotic SAEs, including 1 event considered related to vaccination by the investigator:

- A 35-year-old healthy female on oral contraceptives experienced an SAE of deep vein thrombosis (DVT) on Day 7 post-booster dose and was treated with anticoagulation and discontinuation of oral contraceptives. On Day 10 post-booster dose she developed worsening swelling and groin pain. A computerized tomography angiogram of the pelvis and abdomen with contrast showed bilateral pulmonary artery emboli, questionable pelvic thrombus on, and extensive left lower extremity DVT extending through pelvic veins into the inferior aspect of the inferior vena cava. She was treated with thrombolysis with residual clot noted on venogram and underwent catheter directed tissue plasminogen activator to remove clots in the abdomen and groin. Despite these interventions and anti-coagulation, she continued to have groin swelling and pain and pelvic and femoral stents were placed. A

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computerized tomography scan of the abdomen and pelvis without contrast demonstrated left lower extremity DVT and extensive clot from femoral to iliac arteries with possible May-Thurner syndrome. She underwent a second catheter directed administration of tissue plasminogen activator with stent placement and venoplasty. The event of DVT and PE resolved. The investigator assessed both events as related to vaccine. FDA assesses the extensive left leg and pelvic deep vein thrombosis and pulmonary embolism as possibly related the vaccine. Confounders include use of an oral contraceptive pill and May-Thurner syndrome, although this diagnosis was not confirmed.

The remaining events were not considered related to vaccine by the investigator and included the following:

- A 49-year-old male with a history of opiate dependence and smoking developed COVID-19 approximately 120 days after the booster dose and then reported SAEs of pulmonary embolism, right ventricular heart strain, acquired thrombocytopenia, unspecified anemia and respiratory failure 147 days post-booster dose and bilateral DVTs 149 days post-booster dose. The investigator assessed the events as not related to vaccine. FDA agrees with the investigator's assessment, due to temporal implausibility and a plausible alternative etiology (COVID-19).
- Three participants reported SAEs of deep vein thrombosis, peripheral artery thrombosis, and subclavian artery thrombosis, respectively. These events all had onset 70 days or more after booster dose, occurred in participants with pre-existing history that predisposed them to events, and were all considered not related to vaccination by the investigator.
- Four participants reported SAEs of pulmonary embolism. One event of pulmonary embolism was reported in a 40-year-old woman at 6 weeks post-partum and 38 days after the booster dose, following recent placement of a Nexplanon (etonogestrel) implant. The remaining events were reported 65 days or more following the booster dose and occurred in participants with pre-existing history or concurrent events that predisposed them to thromboembolic events, and were all considered not related to vaccination by the investigator.

A total of 8 participants reported 13 neurovascular SAEs, none of which were considered related to vaccination by the investigator. Three participants had the onset of the event within 28 days of vaccination:

- A 56-year-old female with a history of hypertension, obesity, atrial fibrillation, hypertensive emergency, and cerebrovascular accident reported an SAE of transient ischemic attack (TIA) on Day 8 post-booster dose.
- A 68-year-old male with a history of dyslipidemia and obesity reported an SAE of a TIA Day 18 days post-booster dose. An MRI of the head showed no evidence of acute ischemia, minimal sequelae of chronic small vessel ischemic disease, and was negative for an acute infarct. The investigator considered that concomitant celecoxib may have provided an alternative etiology for the event.
- A 65-year-old female with a history of hyperlipidemia, hypertension, and CHF reported SAEs of left proximal internal carotid artery dissection, and proximal internal carotid artery thrombus, and cerebrovascular accident on Day 19 days post-booster dose.

Although these 3 participants all experienced neurovascular events within several weeks of vaccination, each had underlying risk factors for stroke and a causal relationship with vaccination cannot be definitively established.

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The remaining 5 participants reported events of cerebrovascular accident, ischemic stroke, and TIA. The events were all reported in participants over 60 years of age, with onset 55 days or more from booster dose vaccination.

As described in the [EUA Review Memorandum](#) for the primary series authorization, the proportion of participants with thrombotic and embolic events was comparable across treatment arms in the pre-crossover period; however, a close temporal relationship to vaccine was more commonly observed following doses of NVX-CoV2373 compared to placebo and an analysis of events limited to 28 days following each dose in both the pre- and post-crossover periods also demonstrated a small imbalance. An imbalance in neurovascular events was observed in the pre-crossover period, although the available data did not clearly demonstrate an association of neurovascular events with NVX-CoV2373. Although the absence of a comparator precludes an assessment of increased frequency of events following booster dose vaccination, thromboembolic and neurovascular events were observed; however, no clear pattern of events was detected to suggest a definitive association with vaccination. The Sponsor previously agreed to include safety outcomes in the two active safety surveillance studies for certain neurovascular and thromboembolic events. These safety outcomes will further evaluate adverse events observed in clinical trials.

Subgroup analysis

SAEs were reported by 1.2% of participants 18 to 64 years of age (n=10747) and by 2.4% of participants ≥65 years of age (n=2010). Cardiac SAE disorders occurred in 0.1% of participants 18-64 compared to 0.3% of participants ≥65 years of age. No new safety concerns were identified based on a review of the SAE data by age. Distribution and frequency of SAEs by race, gender, and ethnicity did not show notable differences.

Deaths

A total of 8 deaths were reported, 1 of which occurred within 28 days of the booster dose:

- A 43-year-old male with a history of alcohol and substance abuse, cirrhosis, and type 2 diabetes mellitus had a fatal cardiac arrest on Day 21 post-booster. The participant was found unresponsive at home, jaundiced, with multiple bruises from a recent fall several weeks earlier. Per the death certificate, the immediate cause of death was cardiac arrest, and underlying causes of death were hepatic cirrhosis and high blood pressure. The investigator assessed the event as not related to vaccine. At this time, there is insufficient information to assess for causality to NVX-CoV2373 and in FDA's assessment, vaccination cannot be definitively excluded as a contributory factor, although this participant had multiple underlying comorbidities.

Two additional fatal cardiac arrests were reported, neither of which was considered related to vaccine by the investigator:

- A 53-year-old male with a history of hypertension, sleep apnea, COPD, congestive heart failure, type II diabetes mellitus, smoking, obesity, and alcohol abuse experienced a seizure and was unresponsive 53 days after the booster dose. The cause of death was cardiac arrest (per Investigator and medical records), seizure with an approximate onset to death of 1 hour, alcohol withdrawal with delirium tremens with an approximate onset to death of 3 days.

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- A 36-year-old female with a history of headaches collapsed at home and experienced a fatal SAE of cardiac arrest 165 days after the booster dose. It was unknown whether an autopsy was performed or if a death certificate was obtained. No further information was available.

Although information on these cardiac arrest events is limited, the latency to onset of the fatal events is not suggestive of a causal relationship to vaccination.

The remaining 5 deaths occurred more than 28 days after booster dose administration and included events of motor vehicle accident (Day 31 post-booster dose), cardiac arrhythmia (Day 34 post-booster dose), sepsis (Day 47 post-booster dose), septic shock (Day 99 post-booster dose), and esophageal adenocarcinoma (Day 143 post-booster dose).

None of the fatal SAEs were assessed by the investigator as related to vaccine. FDA agrees that these events are unlikely to be related to vaccination due to temporal implausibility, underlying conditions, and/or a clear alternative etiology.

6.5.5. Late-Breaking Data

Additional late-breaking data were provided by the Sponsor that included new events through October 11, 2022. Datasets were not provided; therefore, the safety data described below has not been independently verified by FDA.

SAEs/Deaths

An SAE of muscle edema that was assessed as related to vaccination was reported:

- A 51-year-old female initially reported mild pain at the left arm injection site, which was treated with acetaminophen. On Day 7 post-booster dose, the participant reported an SAE of type 1 fibrillary edema in the left biceps muscle and edema of the left biceps longus tendon and left supraspinatus tendon that required physical therapy and treatment with non-steroidal anti-inflammatory drugs. The loss of force in the left arm, which had not improved with physiotherapy, impacted the participant's daily life and employment. The event has been ongoing for approximately 6.5 months and is not resolved.

No plausible alternative etiologies have been identified, and the differential diagnosis includes inflammatory disorders, autoimmune disorders, exercise induced trauma, and exertional rhabdomyolysis. The investigator and the FDA consider this event possibly related to vaccination based on plausible biological mechanism and temporal relationship, although currently available information for this event is insufficient to determine a causal relationship with the vaccine. A review of musculoskeletal events in the Total Booster Set did not reveal any similar events.

Four new additional SAEs occurred in the late-breaking time period, including 2 fatal events. Non-fatal SAEs included nausea and vomiting with onset 13 days post-booster dose attributed to buprenorphine and a perforated ulcer with onset 108 days post-booster dose. Fatal SAEs included fentanyl overdose on Day 229 post-booster dose and an unknown cause of death on Day 217 days post-booster dose in a participant with HIV, diverticulosis, and methamphetamine substance disorder. These SAEs and deaths were assessed as not related to vaccine by the investigator. FDA agrees with this assessment due to temporal implausibility or clear alternative etiology for each SAE.

6.6. COVID-19 Cases Among Booster Participants

Definitions for COVID-19 cases can be found in [Appendix B](#). Of the 298 booster cohort participants, 3 had mild COVID-19 cases with onset ≥ 7 days after the booster. These 3 cases occurred at Days 8-11 after booster vaccination in males between 34 and 37 years of age. Among the 2 participants with SARS-CoV-2 sequence information available, both were Omicron BA.1.1. Outcome information was available for 1 case, which was reported as recovered.

As of March 26, 2022, of the Total Booster Set who received a booster dose following completion of a primary series (n=12,738), 4 had COVID-19 cases with onset ≥ 7 days after the booster dose (3 severe cases and 1 mild case). The severe cases occurred at 8-12 days after booster vaccination in a 38 year-old male, 46 year-old female, and a 72 year-old diabetic male, respectively. The mild case occurred 11 days after booster in a 63-year-old female. Among the 2 participants with SARS-CoV-2 sequence information available, both cases were severe and both strains were identified as Omicron BA.1.1. All 4 participants recovered without sequelae. Information on COVID-19 cases in the Total Booster Set were not independently verified by FDA, as source documentation and datasets were not provided.

6.7. Summary of Immunogenicity and Safety Data

The clinical data submitted to this EUA amendment come from ongoing Study 301, which is also the source of clinical data that supported the authorization of the 2-dose primary series in individuals 12 years of age and older. In this study, a NVX-CoV2373 booster dose was administered at least 6 months after completion of primary vaccination series. The immunogenicity and safety of NVX-CoV2373 was assessed in a subset of 298 booster recipients selected from 7 US sites.

Vaccine effectiveness was inferred based on immunobridging analyses in a subset of 239 Phase 3 NVX-CoV2373 booster dose recipients using prespecified non-inferiority criteria to compare MN_{50} GMTs and the difference in SCRs against the reference strain (USA_WA1/2020, Wuhan-like) at 28 days post- NVX-CoV2373 booster dose vs. 14 days post-primary series. The GMT ratio (Booster/Primary series) was 3.4 and the lower bound of the 95% CI was 2.8, which met the corresponding success criteria of >0.67 and a GMT ratio estimate >0.83 . SCRs against the original SARS-CoV-2 virus strain neutralizing antibodies at 28 days after the booster dose vs. those values 14 days after the primary series was -9.2%, and the lower bound of the 95% CI was -14.4%, which did not meet the corresponding success criterion of $>-10\%$. The SCR from pre-booster dose to 28 days post-booster dose (85.4%) was lower than the SCR after the primary series (from baseline pre-Dose 1 to 1 month post-Dose 2) (94.6%), reflecting that a ≥ 4 -fold increase in titer is more difficult to achieve from a booster dose administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination. An additional descriptive post hoc analysis evaluated SCRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. The booster dose SCR, with seroconversion defined as at least a 4-fold rise relative to the time of first dose, was 98.3%. The difference in SCRs in this post-hoc analysis was 3.8% (95% CI 2.0%, 7.0%). Additional descriptive exploratory immunogenicity data evaluating neutralizing antibody titers elicited by the booster dose against the reference strain (wild-type) of SARS-CoV-2 and Delta and Omicron variants demonstrated increases in titers following a booster dose of NVX-CoV2373.

Overall, local and systemic reactogenicity events in the 298 participants were reported by a larger proportion of participants following a booster dose compared to both primary series

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doses. Among NVX-CoV2373 booster recipients, the frequencies of solicited adverse events generally were lower among the older adults ≥ 65 years of age compared with the adults 18 through 64 years of age; however, the small number of the older adults age group limits any conclusions about the reactogenicity profile of the booster dose. Unsolicited AEs were comparable to those seen with the primary series of vaccination, including three related AEs of lymphadenopathy, injection site pain, and neuralgia.

Of the 12,738 participants who received a NVX-CoV2373 booster through March 26, 2022, 173 participants reported SAEs (1.4%), 5 of which were considered by FDA as at least possibly related to booster dose vaccination: autoimmune hepatitis, muscle edema, cellulitis, extensive deep vein thrombosis and pulmonary embolism, and an event adjudicated as non-ST elevation myocardial infarction (with features of myocarditis). Myocarditis/pericarditis are known uncommon serious risks associated with the NVX-CoV2373 primary series and the details of the non-ST elevation myocardial infarction are consistent with these AEs seen with NVX-CoV2373 and described in the fact sheets. Eight deaths were reported, none of which were causally related to NVX-CoV2373.

Although review of the safety data is limited by the lack of a comparator group, no additional new safety concerns were identified following review of the available data.

In conclusion, the clinical data from Study 301 support NVX-CoV2373 as a first booster dose administered at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 Vaccine in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.

7. FDA Review of Other Information Submitted

7.1. Heterologous Booster Safety and Immunogenicity Data From COV-BOOST Study

Data in support of a heterologous booster consists of a publication of a clinical study by Munro et al.²⁴ Source documentation, datasets from this study, and details on the methodology and validation of assays were not provided for FDA review. In this Phase 2, randomized, controlled investigator-initiated trial conducted in the United Kingdom, a COVID-19 booster dose (1 of 7 COVID-19 vaccines, including NVX-CoV2373) or comparator (quadrivalent meningococcal conjugate vaccine; MenACWY) was administered to a total of 2,878 healthy adults ≥ 30 years of age who completed primary vaccination with another authorized or approved COVID-19.²⁴ In the study group who received a NVX-CoV2373 booster dose, 114 participants had received a two-dose primary series with a COVID-19 vaccine authorized/approved in the United States (Pfizer-BioNTech COVID-19 Vaccine; BNT162b2). NVX-CoV2373 was administered at a median of 105 days (range: 93-147 days) after completion of a BNT162b2 primary series. Neutralizing antibody titers against SARS-CoV-2 Wild Type Virus were measured pre-booster and 28 days after booster vaccination.

Demographic characteristics for the participants are shown in [Table 16](#). Overall, of those who received a primary series with BNT162b2 and a NVX-CoV2373 booster (n=114), the majority of the population was White (95.6%), 57% were female, and 57% were <70 years of age. Cardiovascular comorbidity was the most common of the 3 reported comorbidities (cardiovascular, respiratory, and diabetes) at 30.7%.

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Table 16. Demographic and Baseline Characteristics, COV BOOST Study

Characteristic	Primary Series: BNT162b2 Booster: MenACWY Comparator N=118	Primary Series: BNT162b2 Booster: NVX-CoV2373 N=114
Age, years	--	--
Mean (SD)	63.1 (16.9)	62.1 (16.4)
Median (IQR)	62.4 (49.4-78.5)	62.7 (48.0-75.5)
Interval between first and second doses, days (range)	41.0 (21.0-68.8)	42.0 (23.2-65.5)
Interval between second and third doses, days (range)	104.5 (95.2-146.0)	104.5 (93.0-146.8)
Age group, n (%)	--	--
<70 years	66 (55.9%)	65 (57.0%)
≥70 years	52 (44.1%)	49 (43.0%)
Sex, n (%)	--	--
Female	69 (58.5%)	65 (57.0%)
Male	49 (41.5%)	49 (43.0%)
Occupation, n (%)	--	--
Health worker	57 (48.3%)	59 (51.8%)
Other	61 (51.7%)	55 (48.2%)
Ethnicity, n (%)	--	--
White	106 (89.8%)	109 (95.6%)
Black	1 (0.8%)	0
Asian	10 (8.5%)	5 (4.4%)
Mixed	1 (0.8%)	0
Other	0	0
Not given	0	0
Comorbidities, n (%)	--	--
Cardiovascular	37 (31.4%)	35 (30.7%)
Respiratory	14 (11.9%)	15 (13.2%)
Diabetes	11 (9.3%)	7 (6.1%)

Source: Adapted from Table 2 from Munro et al. 2021.
Abbreviations: BNT162b2=Pfizer-BioNTech COVID-19 Vaccine;
IQR=interquartile range; vaccine

In participants who completed a BNT162b2 primary series, immune responses were assessed using a pseudotype virus neutralizing assay and a live virus neutralizing assay. Using a live virus assay, the normalized NT₈₀ GMT was 1,454 after a NVX-CoV2373 booster dose, compared to a GMT of 531 in the control group; the GMR (NVX-CoV2373 booster/control) was 2.65. Using a pseudotype virus neutralizing assay, the NT₅₀ (Delta) GMT was 766 after a NVX-CoV2373 booster, compared with a GMT of 157 in the control group; the GMR (NVX-CoV2373 booster/ control) was 5.39 ([Table 17](#)).

Table 17. Immune Responses at 28 Days After NVX-CoV2373 Booster Dose in Participants Completing a BNT162b2 Primary Series, COVID-19-Naïve mITT Population, COV Boost Study

Parameter	Primary Series: BNT162b2 Booster: MenACWY comparator N=111	Primary Series: BNT162b2 Booster: NVX-CoV2373 N=103¹
PsVNA (wild-type), NT ₅₀	--	--
GMT*	157 (129-192; n=111)	766 (624-939; n=94)
GMR†	Ref	5.39 (4.35-6.67)

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Parameter	Primary Series: BNT162b2 Booster: MenACWY comparator N=111	Primary Series: BNT162b2 Booster: NVX-CoV2373 N=103¹
PVNA (Delta), NT ₅₀	--	--
GMT*	37.9 (30.5-47.1; n=111)	165 (131-209; n=89)
GMR†	Ref	4.94 (3.86-6.31)
LVN antibody, normalized NT ₈₀	--	--
GMT*	531 (377-748; n=38)	1454 (1060-1995; n=24)
GMR†	Ref	2.65 (1.77-3.98)

Source: Adapted from Table 5 from Munro et al, 2021.

Abbreviations: BNT=BNT162b2 vaccine, Pfizer–BioNTech; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; ELU=ELISA laboratory units; GMC=geometric mean concentration; GMR=geometric mean ratio; GM=geometric mean; GMT=geometric mean titer; LVN=live virus neutralization; mITT=modified intent-to-treat; NT₅₀=50% neutralizing antibody titer; NT₈₀=80% neutralizing antibody titer; PVNA=pseudotype virus neutralizing antibody

1. Of the 114 participants, 11 participants were excluded due to previous COVID-19 at baseline or withdrawal before Day 28.

* Data are GM (95% CI; number of samples available).

† GMRs of the study vaccines were calculated by comparing control groups after adjusting for age group, site, baseline anti-spike IgG, interval between first and second dose, and interval between second and third dose

Note: The methods used for immunogenicity assays include methods for SARS-CoV-2 pseudotype virus neutralisation assays (PVNA, Nexelis, Laval, QC, Canada), live SARS-CoV-2 virus neutralization (LVN, lineage Victoria/01/2020) was determined by microneutralization assay (MNA) at Porton Down. No information regarding the assays used in the study were submitted or reviewed by the FDA.

Safety data from NVX-CoV2373 booster recipients did not show evidence of increased local or systemic reactogenicity relative to the comparator group (MenACWY). Limited information on AESIs and SAEs was provided in the publication. Among the NVX-CoV2373 booster participants, 2 SAEs were reported. No AESIs were reported. SAEs included the following:

- An 83-year-old participant with a history of hypertension reported an SAE of pericarditis 31 days after a booster dose (one half of the standard dose of NVX-CoV2373). He was hospitalized for 1 day after he experienced difficulty breathing and was discharged with treatment with colchicine for 3 months. His symptoms improved after 7 days, and the event resolved in 1 month. The study investigator assessed the pericarditis as not related to NVX-CoV2373 vaccine. Although the clinical features of this pericarditis event is similar to events seen in clinical trials, the lack of immediate temporal relationship makes a causal relationship to vaccine less likely.
- A 58-year-old participant (sex not reported) reported an SAE of urinary tract infection.

No other adverse events of concern were identified following FDA review of the safety events described in the published article.

7.2. Post-Authorization/Postmarketing Reports of Myocarditis/Pericarditis

Worldwide post-authorization (or postmarketing) data also provide evidence for increased risks of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted. Foreign postmarketing reports of myocarditis and pericarditis emerged prior to initial US authorization and contributed to the FDA’s decision to ask the Sponsor to list “myocarditis and pericarditis” as an Important Identified Risk in the US Pharmacovigilance Plan (CBER IR #35, sent May 24, 2022). Since then, the Sponsor continued to monitor postmarketing reports of myocarditis and pericarditis and on August 3, 2022, the Sponsor classified myocarditis and pericarditis as a confirmed safety signal, prompting updates to their Core Company Data Sheet and core Risk Management Plan. The Sponsor assessed postmarketing reports of myocarditis and pericarditis in each of their Monthly Safety Summary

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Reports (MSSRs), including the most recently reviewed MSSR (#7) covering reporting period August 1, 2022, to August 31, 2022 (IND 22430/0.355).

In MSSR #7, the Sponsor used two different search strategies to identify cases of myocarditis and pericarditis in their postmarketing safety database. First, the Sponsor used a “narrow search strategy” to retrieve cases to be used in Observed-to-Expected (O/E) analyses. For the “narrow search”, the Sponsor used the narrow SMQ “Noninfectious myocarditis/pericarditis” as well as the High Level Terms (HLT) “Noninfectious myocarditis” and “Noninfectious pericarditis.” Next, the Sponsor used a “broad search strategy” to retrieve cases for evaluation against Brighton Collaboration criteria. For the “broad search”, the Sponsor used the broad SMQ “Noninfectious myocarditis/pericarditis” in addition to the following HLTs: “Infectious myocarditis”, “Infectious pericarditis”, “Noninfectious myocarditis”, and “Noninfectious pericarditis.”

Using the “narrow search strategy,” the Sponsor identified 55 individual case safety reports (ICSRs) for myocarditis and pericarditis. These 55 ICSR included 56 AEs coded to PTs Pericarditis (n=35); Myocarditis (n=13); Myopericarditis (n=6); and Carditis (n=2). Of the 36 AEs with reported time to onset, 35 fell within a window of 0-18 days postvaccination. Observed-to-expected (O/E) analyses showed statistically significant elevated O/E rate ratios for all risk windows (0-7 days, 0-14 days, 0-30 days, and 0-42 days) with the highest rate ratio for the risk window 0-7 days (14.90, 95% CI 10.95 – 19.81). In addition, O/E rate ratios remained statistically significantly elevated when evaluating only AEs reported by a healthcare professional. Lastly, when stratified by age and sex, O/E rate ratios were statistically significantly elevated for males overall, females overall, and several age/sex subgroups. However, the numbers became sparse with stratification, creating imprecise estimates for most age/sex strata.

Using the “broad search strategy,” the Sponsor retrieved 85 ICSR, which includes the 55 ICSR identified in the narrow search above. Of these 85 ICSR, 32 met criteria for Brighton Collaboration case definition Levels 1-3 for myocarditis and pericarditis. Among these 32 adjudicated cases, a majority were male (56.3%), and age groups ranged from 18 years to greater than 60 years. Most cases occurred within 14 days of vaccination (59.4%) and most outcomes were reported as “Not Recovered / Not Resolved” (68.8%).

Regarding FDA post-authorization experience, a search of the Vaccine Adverse Event Reporting System (VAERS) database (using the Sponsor’s broad search strategy described above) on October 13, 2022, revealed 2 reports of pericarditis from a US source: 1) a 46-year-old male received a first dose of Novavax COVID-19 Vaccine, Adjuvanted and an unspecified time later experienced pericarditis. A cardiac MRI done 3 weeks after vaccination showed “Small circumferential simple pericardial effusion. Minimal late enhancement of the pericardium.”; and 2) a 55-year-old female received dose 1 of Novavax COVID-19 Vaccine, Adjuvanted and 5 days later was hospitalized for pericarditis. The first case meets CDC’s case definition for pericarditis. The second case will be adjudicated pending follow up information. The VAERS database query also returned 14 reports of myocarditis or pericarditis from foreign sources: Pericarditis (n=12); Myocarditis (n=1); Myopericarditis (n=1). Nine of these cases were male and five were female and their ages ranged from 24 to 67 years. The time to onset (when reported) ranged from one to 21 days postvaccination. When dose number was specified, it included dose numbers 1, 2, and a “booster” dose. The outcome was reported as recovered for

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two cases. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated with initially subclinical myocarditis (and if it is what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

7.3. Pharmacovigilance Activities

The Sponsor submitted an updated Pharmacovigilance Plan (Version 1.1, dated September 20, 2022) to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine, Adjuvanted. The Sponsor included anaphylaxis and myocarditis and/or pericarditis as important identified risks. Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease is an important potential risk. 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 are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Serious adverse events (irrespective of attribution to vaccination)
- Cases of myocarditis
- Cases of pericarditis
- Cases of Multisystem Inflammatory Syndrome in adults and children
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and submit periodic safety reports in accordance with a reporting interval and due date agreed upon with the Office of Biostatistics and Pharmacovigilance. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

The Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following 5 planned surveillance studies.

- **Pregnancy Exposure Registry:** The Sponsor plans to use the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) to conduct a multi-country, observational, prospective, cohort study of women vaccinated during pregnancy with a COVID-19 vaccine to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with the Novavax COVID-19 Vaccine. The planned study duration is 48 months for enrollment and follow-up of participants.

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- **US Active Follow-Up for Safety:** This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in adults 18 years of age and older in the real-world setting in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30 months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the US.
- **UK Active Follow-Up for Safety:** This is an active safety surveillance study to evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 Vaccine in individuals 12 years of age and older in the real-world setting in the United Kingdom (UK). The Sponsor plans to use the Clinical Practice Research Datalink and associated linked databases for this study. The study design includes two methods: 1) a self-controlled case series design and 2) a retrospective comparative matched cohort study design. The planned study duration is 30 months following receipt of regulatory authorization of the Novavax COVID-19 Vaccine in the UK.
- **US Real World Effectiveness Study:** This study is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine in preventing SARS-CoV-2 infection in adults 18 years of age and older in the US. The Sponsor plans to use a large US-based insurance claims database and/or electronic health records database. The study design is a retrospective comparative cohort study design. The planned study duration is 30 months following FDA concurrence on the final study protocol.
- **European Real World Effectiveness Study:** This is a real-world effectiveness study to assess the effectiveness of the Novavax COVID-19 Vaccine against hospitalization due to laboratory-confirmed SARS-CoV-2 in multiple European countries. The Sponsor plans to use COVIDRIVE, a multi-stakeholder, public-private partnership program, as the data source. The study is a prospective, hospital-based case-control study using a test-negative design. The planned duration of the study is a minimum of one year with an expected study duration of two years.

With the exception of the pregnancy exposure registry, the Sponsor agreed to update the protocols for each post-authorization study to include adolescents 12 to <18 years of age.

The Sponsor agreed to update the post-authorization study protocols to include evaluation of safety and effectiveness of a booster dose in individuals 18 years of age and older.

The Sponsor agreed to include “autoimmune hepatitis” as a safety outcome in the two active surveillance safety studies. In addition, the Sponsor agreed to provide an assessment of postmarketing cases of both “autoimmune hepatitis” as well as “hepatitis and liver injury” in their Monthly Safety Summary Reports (MSSRs).

Reporting to VAERS and Novavax

Providers administering the Novavax COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to the extent feasible, report to Novavax, the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of myocarditis
- Cases of pericarditis

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- Cases of Multisystem Inflammatory Syndrome in adults and children
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys to help COVID-19 vaccine recipients monitor for and report side effects. The system also will provide telephone follow-up to anyone who reports medically important adverse events. Responses indicating missed work, inability to do normal daily activities, or receipt of care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

7.4. Clinical Assay Information

The measurement of SARS-CoV-2-neutralizing antibodies induced by the NVX-CoV2373 vaccine is performed by a microneutralization (MN) assay. This assay was used in testing paired serum samples obtained after vaccination with the NVX-CoV2373 primary series, followed by administration of a homologous (Wuhan strain) booster to generate data for immunobridging analyses. In the assay, serum samples obtained from clinical studies are tested for the ability to block the infection of Vero E6 cells by a clinical isolate of the prototype SARS-CoV-2 (hCoV-19/Australia/VIC01/2020) *in vitro*. The MN assay for SARS-CoV-2 prototype strain was validated at 360 Biolabs (Melbourne, Australia), for precision, sensitivity (lower limit of quantitation and upper limit of quantitation), specificity, selectivity, and dilutional linearity. In addition, matrix effect, robustness, and sample stability were evaluated in the validation study. COVID-19 convalescent serum samples, pre-COVID-19 serum samples, and incurred serum samples from the Phase 1 clinical evaluation of NVX-CoV2373 were used in the validation study. Data from the validation study show that acceptance criteria were met for each assay-validation parameter, supporting the utility of the MN assay in measuring the levels of SARS-CoV-2-neutralizing antibody induced in vaccine recipients.

In addition, the neutralization of SARS-CoV-2 variants of concern (Delta, Omicron BA.1 and Omicron BA.5) was evaluated in exploratory immunogenicity analyses. An MN assay, similar to the one for the prototype SARS-CoV-2 described above, was used as a fit-for-purpose assay in testing serum samples for the neutralization of Omicron BA.1 (SARS-CoV-2-hCoV-19/Australia/VIC29890/2021). The BA.1 MN assay has since been validated using convalescent serum samples from individuals infected with Omicron BA.1 sub-lineage (sequence-confirmed) for precision, sensitivity, selectivity, and dilutional linearity. Similarly, MN assay for the Delta strain has been validated but validation of a BA.5 MN assay is in progress.

In additional exploratory immunogenicity analyses, neutralization of Wuhan (D614G strain), Delta, Omicron BA.1, and Omicron BA.5 was evaluated at Monogram Biosciences, using pseudotype virus neutralization assay(s) (pVNAs). The pVNA was successfully validated for Wuhan (D614G strain) using serum samples collected from individuals infected with the Wuhan strain, as well as with incurred serum samples from individuals who received the prototype NVX-CoV2373 vaccine. The pVNA was updated and separately validated for Delta and BA.1, using post-infection convalescent serum samples (sequence-matched) from individuals known to have been infected with Delta or Omicron BA.1, respectively. Delta and BA.1 pVNAs are deemed validated to quantitate the neutralizing antibody titers to the matched variant. The Sponsor has been advised to validate the pVNA for BA.5, which has not been validated at this time. In summary, exploratory assessment of neutralizing antibody in variant-specific pVNAs

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provide supportive evidence of neutralizing activity against SARS-CoV-2 variants in serum samples obtained from individuals who received the NVX-CoV2373 homologous booster dose.

The data submitted to demonstrate that NVX-CoV2373 increases the levels of neutralizing antibody when administered as a booster dose in prior recipients of the Pfizer-BioNTech mRNA COVID-19 vaccine primary series (COV-BOOST; heterologous booster study) were obtained using a SARS-CoV-2 pVNA performed at Nexelis (Laval, Quebec, Canada) and live virus neutralization (LVN) assay performed at Porton Down (United Kingdom). Information on these assays was not submitted for FDA review.

7.5. Inspection of Clinical Study Sites

The review team decided that Bioresearch Monitoring inspections are not needed to support the review of this EUA amendment.

7.6. EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

8. Benefit/Risk Assessment in the Context of the Proposed Use Under EUA

8.1. Known and Potential Benefits

The NVX-CoV2373 vaccine administered as a 2-dose primary series was demonstrated to be efficacious against COVID-19 in an ongoing Phase 3 clinical trial that supported Emergency Use Authorization). The clinical benefit of a booster dose administered at least 6 months after completion of the primary series would be related to the restoration of high vaccine effectiveness (or more durable vaccine effectiveness) in individuals for whom protective immunity has waned. In considering the statutory criteria for EUA, the relevant clinical benefit would be related specifically to protection against serious outcomes of COVID-19. The evidence for the benefit of a booster dose is therefore derived from: 1) data to support waning protection against serious outcomes of COVID-19 in those populations for which use of a booster dose under EUA is being considered; 2) data to infer effectiveness of the booster dose based on an evaluation of 50% neutralizing antibody GMTs against the reference SARS-CoV-2 strain (recombinant USA-WA1/2020) elicited at 28 days after the booster dose compared to GMTs at 14 days post-primary series among booster dose recipients; and 3) data to support the effectiveness of a booster dose against currently circulating SARS-CoV-2 variants.

With regard to evidence to support waning protection against serious outcomes of COVID-19, results from observational studies (although not independently verified by FDA) that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time. Based on the available evidence, it appears that primary vaccination with the COVID-19 vaccines available for use in the United States does reduce the risk of serious disease, including hospitalization and death due to the Omicron variant, and the recent administration of a first booster dose of an mRNA COVID-19 vaccine appears to be associated with a notably lower likelihood of breakthrough infection and COVID-19 associated

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hospitalization compared to primary vaccination alone.²⁵ The emergence of the highly transmissible Delta and Omicron variants of SARS-CoV-2 led to the administration of booster doses to individuals who have already received primary vaccination in an effort to enhance immunity and thus sustain protection from COVID-19.

With regard to evidence to support the effectiveness of a NVX-CoV2373 booster dose against the reference SARS-CoV-2 strain and currently circulating SARS-CoV-2 variants, the successful booster dose immunobridging analysis from Study 301, based on neutralizing antibody GMTs against the reference strain (recombinant USA_WA1/2020), support inference of the booster dose effectiveness in individuals ≥ 18 years of age who completed a primary series of NVX-CoV2373. However, the difference in percentages of participants with booster seroconversion and primary seroconversion did not meet the immunobridging success criterion. The SCR from pre-booster dose to 28 days post-booster dose (85.4%) was lower than the SCR after the primary series (from baseline pre-Dose 1 to 1 month post-Dose 2) (94.6%), reflecting that a ≥ 4 -fold increase in titer is more difficult to achieve from a booster dose administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination. An additional descriptive post hoc analysis evaluated SCRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. The booster dose SCR, with seroconversion defined as at least a 4-fold rise relative to the time of first dose, was 98.3%, with a difference in SCRs in of 3.8% (95% CI 2.0%, 7.0%). Additional exploratory immunogenicity analyses evaluating neutralization of the Delta, Omicron BA.1, and BA.5 sublineages support the potential for the booster dose to provide additional protection against these variants, although limitations in the data include small numbers (n=17-18) of samples and use of a non-validated assay for the BA.5 sublineage.

Effectiveness of a NVX-CoV2373 heterologous booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 vaccine is inferred from immunogenicity data reported from an independent study conducted in the United Kingdom (COV-BOOST study), where a booster response to NVX-CoV2373 was demonstrated with individuals who received BNT162b2 for their primary series.

8.2. Uncertain Benefits/Data Gaps

Effectiveness of booster dose against SARS-CoV-2 variants of concern

As summarized above, immunogenicity data to support effectiveness of the booster dose against the Omicron variant are limited to exploratory analyses in a small number of study participants, some of which employed non-validated assays (BA.5 sublineage). At this time, data are lacking to directly demonstrate efficacy of a booster dose against clinical disease outcomes from SARS-CoV-2 Omicron variant infection. Furthermore, other variants could emerge in the future, against which the NVX-CoV2373 booster dose may be less effective.

Booster dose durability of protection

Immunogenicity analyses were conducted 28 days post-booster; therefore, it is not possible to assess sustained effectiveness over a period of time longer than a month.

Effectiveness of booster dose against viral shedding and transmission

The effectiveness of a booster dose against transmission of SARS-CoV-2 from individuals who are infected despite vaccination has not yet been established.

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Effectiveness of booster dose against long term effects of COVID-19 disease

Prevention of cases of symptomatic COVID-19 by a booster dose will likely result in prevention of some COVID-19 cases with long-term sequelae. However, additional studies are needed to verify this potential benefit.

Future effectiveness of booster dose as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The evolution of the pandemic characteristics, such as increased attack rates, emergence of new variants, and/or the effect of coinfections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of booster dose effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

8.3. Known and Potential Risks

Overall, local and systemic reactogenicity events were reported by a larger proportion of participants following a booster dose compared to both primary series doses. Among NVX-CoV2373 booster recipients, the frequencies of solicited adverse events generally were lower among the older adults ≥ 65 years of age compared with the adults 18 through 64 years of age; however, the small number of individuals in these groups limits any definitive conclusions about the reactogenicity profile of the booster dose.

Myocarditis/pericarditis are known uncommon serious risks associated with the NVX-CoV2373 primary series. One case of myocarditis was reported by a 28-year-old male participant 3 days after a booster dose of NVX-CoV2373. Available data from mRNA COVID-19 vaccines suggest that myocarditis/pericarditis risk is greatest in males under the age of 40 (and specifically males 16-17 years of age) following the second primary series dose.

Four additional SAEs were considered potentially related to booster dose vaccination, including autoimmune hepatitis, muscle edema, cellulitis, and extensive deep vein thrombosis and pulmonary embolism. Currently available information for these events is insufficient to determine a causal relationship with the vaccine.

The safety of an NVX-CoV2373 booster dose in individuals who completed a primary vaccination with another authorized or approved COVID-19 vaccine (heterologous booster dose) was inferred from the COV-BOOST study, which enrolled participants who had previously received a primary series vaccination of BNT162b2. Reported adverse reactions through 28 days following an NVX-CoV2373 booster dose after completion of the BNT162b2 primary series did not identify any new safety concerns as compared with adverse reactions reported following two doses of NVX-CoV2373 given as a primary series.

8.4. Uncertain Risks/Data Gaps

Adverse reactions that are very uncommon or that require longer follow-up to be detected

It is unknown if the risk of myocarditis/pericarditis and hepatic events/autoimmune hepatitis would be similar, increased, or decreased following a booster dose of NVX-CoV2373 as compared to the primary series. In addition, the uncertainty around the risk of hepatic events and myocarditis/pericarditis following a booster dose as described above, the duration of safety follow-up, and the size of the available booster dose safety database limit the ability to detect the emergence of rare adverse reactions, which may only be identified with broader use and

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more prolonged safety follow-up. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Safety of booster dose in certain subpopulations

No clinical safety data for a booster dose are available at this time for certain subpopulations, such as pediatric populations less than 18 years of age or pregnant or lactating individuals. For pregnant or lactating individuals, available safety data from use of the primary series do not raise specific safety concerns about extrapolating the safety of a booster dose from data in non-pregnant, non-lactating individuals.

Table 18 Assessment of NVX-CoV2373 With the Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	<ul style="list-style-type: none"> • COVID caused by SARS-CoV-2 has been responsible for 96 million cases and 1 million deaths in the US. • There has been a succession of variants (Delta, Omicron BA.1, BA.4, and most recently BA.5) that have led to a reduction in vaccine effectiveness. • Although the available COVID-19 vaccines based on the original (ancestral) strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased. 	<ul style="list-style-type: none"> • COVID-19 is a serious disease associated with significant morbidity and mortality from initial infection and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals. • Certain available COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease. However, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals.
Current Treatment Options	<ul style="list-style-type: none"> • Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity. • There are four approved or authorized COVID-19 vaccines (two mRNA-based, one non-replicating viral vector, and one protein-based, adjuvanted); these are all effective as primary series, and the bivalent mRNA-based and non-replicating viral vector vaccines may be effective as boosters. • VRBPAC voted on June 28, 2022, 19-2 in favor of utilizing bivalent mRNA booster vaccines with Wuhan and Omicron BA.5 strains. There was a general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. • As of October 12, 2022, in the United States, about half of the individuals who completed their primary series vaccines have not received their first booster dose. 	<ul style="list-style-type: none"> • Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID). • Vaccines play an important role in pandemic control and provide important protection.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • The immunogenicity and safety of booster vaccines against Beta, Delta, and Omicron BA.1 variants were previously evaluated by both current mRNA vaccine manufacturers; however, these vaccines were not deployed in the US because of SARS-CoV-2 variant evolution. • Bivalent mRNA booster vaccines were authorized for emergency use on August 31, 2022. • NVX-CoV2373 is a protein-based, adjuvanted vaccine authorized for the primary series of COVID-19 vaccination. • Immunobridging analyses from the clinical study and immunogenicity data from an independent UK study (COV-BOOST) support inference of the NVX-CoV2373 booster dose effectiveness in individuals ≥ 18 years old. • People may seek an alternative vaccine to the mRNA platform or the mRNA bivalent booster vaccine. • Uncertainty about the translation of the magnitude of the increase in antibody response in humans into effectiveness against COVID-19 outcomes, including symptomatic and serious disease. 	<ul style="list-style-type: none"> • The totality of the available evidence indicates that administration of Novavax COVID-19 Vaccine, Adjuvanted as a first booster dose to individuals 18 years of age and older could potentially increase the broad immune response against SARS-CoV-2 variants. • Administration of Novavax COVID-19 Vaccine, Adjuvanted is appropriate for those individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and for those individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.
Risk and Risk Management	<ul style="list-style-type: none"> • Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and prior booster doses. • Within a week after a second dose of vaccine or booster vaccination with NVX-CoV2373, myocarditis and pericarditis have been observed. • One event of each of autoimmune hepatitis, cellulitis, muscle edema, extensive deep vein thrombosis and pulmonary embolism, and non-ST segment MI was observed that could be plausibly related to booster dose of NVX-CoV2373. • The event of non-ST segment MI has already been described in the fact sheet. 	<ul style="list-style-type: none"> • No other new safety signals were identified compared to the primary vaccination series with Novavax COVID-19 Vaccine, Adjuvanted. • Post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge.

8.5. Conclusions Regarding Benefit-Risk

For individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine, the known and potential benefits of the NVX-CoV2373 booster dose outweigh the known and potential risks of the first booster dose, considering the totality of available evidence and the outstanding uncertainties.

During the current wave of COVID-19 caused in large part by the BA.5 sublineage, administration of a COVID-19 vaccine booster dose is expected to have a favorable benefit-risk profile, potentially not only restoring protection against serious outcomes from COVID-19, but also by reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome. Furthermore, the NVX-CoV2373 booster dose may provide broader protection against COVID-19 variants, which may help protect against future emerging variants.

FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. Although the armamentarium for COVID-19 is robust, additional effective treatment and preventative options that provide greater flexibility in meeting patients' individual needs are needed. Although bivalent mRNA booster vaccines that include an Omicron component were authorized for emergency use on August 31, 2022, there may be individuals for whom the mRNA bivalent booster vaccines are not accessible or clinically appropriate. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted booster dose will provide an alternative for these individuals.

9. Overall Summary and Recommendations

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in [Section 2](#) of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- The scientific evidence available to support this EUA request includes clinical safety and immunogenicity data from Study 301 which was designed to evaluate a NVX-CoV2373 booster dose administered at least 6 months after a NVX-CoV2373 primary series.
- Based on the totality of scientific evidence available, the Novavax COVID-19 Vaccine, Adjuvanted—when administered as a first booster dose to individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine—may be effective in preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2. As summarized in [Section 6](#), vaccine effectiveness was inferred based on immunobridging analyses against the reference strain. The pre-specified success criteria were met for GMT ratio (3.4; 95% CI: 2.8, 4.0) but not in the difference in seroconversion rates for the booster dose compared to the 2-dose primary series (-9.2%; 95% CI: -14.4%, -4.5%). The seroconversion rate from pre-booster dose to 28 days post-booster dose (85.4%) was lower than the seroconversion rate after the primary series (from baseline pre-Dose 1 to 1 month post-Dose 2) (94.6%), reflecting that a >4-fold increase in titer is more difficult to achieve from a booster dose

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administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination.

- Based on the immunogenicity data summarized in [Section 6](#) of this review and assessment of benefits and risks in [Section 7](#) of this review, the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted outweigh the known and potential risks when used as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate and in individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae. Known and potential risks include generally self-limited common local and systemic adverse reactions and rarely myocarditis, and plausible relationship of autoimmune hepatitis, injection arm cellulitis, deep vein thrombosis and pulmonary embolism, and muscle edema to NVX-CoV2373 booster vaccination, although information is limited.
- Comirnaty and Spikevax are the only FDA-approved vaccines indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. No COVID-19 vaccine is currently approved for use as a booster dose.
- The Novavax COVID-19 Vaccine, Adjuvanted would provide an alternative booster dose option to the following individuals who have received a homologous or heterologous primary series vaccination: individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. Use of the Novavax COVID-19 Vaccine, Adjuvanted, a vaccine based on a non-mRNA platform, as a first booster dose in a specific subpopulation of individuals who would otherwise not receive a first booster dose of a COVID-19 vaccine is supported by available safety and immunogenicity data and the potential of Novavax COVID-19 Vaccine, Adjuvanted to restore waning VE, including against severe disease and hospitalization associated with Omicron.
- The Novavax COVID-19 Vaccine, Adjuvanted is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older.

The review team therefore recommends authorization of the Novavax COVID-19 Vaccine, Adjuvanted under EUA for use as a booster dose administered at least 6 months after a homologous or heterologous primary series to individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.

10. Appendix A. Adverse Events of Special Interest

Table 19. Adverse Events of Special Interest/Potential Immune-Mediated Medical Conditions, Study 301

Category	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory disorders	Acute disseminated encephalomyelitis (including site-specific variants: e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyzes/paresis (e.g., Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis.
Musculoskeletal and connective tissue disorders	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome.
Vasculitides:	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and ANCA-positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis).
Gastrointestinal disorders	Crohn's disease, celiac disease, ulcerative colitis, ulcerative proctitis.
Hepatic disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis.
Renal disorders	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis).
Cardiac disorders	Autoimmune myocarditis/cardiomyopathy.
Skin disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome.
Hematologic disorders	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia.
Metabolic disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, new onset Hashimoto thyroiditis, diabetes mellitus type 1, Addison's disease.
Other disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Source: Adapted from protocol 2019nCoV-301 Table 11. IND 22430.

Abbreviations: ANCA=anti-neutrophil cytoplasmic antibody; CREST=calcinosis, Raynaud's phenomenon; esophageal dysmotility; sclerodactyly, telangiectasia; IgA=immunoglobulin A; MedDRA=Medical Dictionary for Regulatory Activities

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11. Appendix B. Case Definitions

Table 20. COVID-19 Case Definitions

Severity	Case Definition
Mild	<ul style="list-style-type: none"> • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough OR ≥2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalized muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhea
Moderate	<ul style="list-style-type: none"> • High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days) • Any evidence of significant LRTI: <ul style="list-style-type: none"> ○ Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) ○ Tachypnea: 24 to 29 breaths per minute at rest ○ SpO₂: 94% to 95% on room air ○ Abnormal chest X-ray or chest computerized tomography consistent with pneumonia or LRTI ○ Adventitious sounds on lung auscultation crackles/rales, wheeze, rhonchi, pleural rub, stridor)
Severe	<ul style="list-style-type: none"> • Tachypnea: ≥30 breaths per minute at rest • Resting heart rate ≥125 beats per minute • Oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mm Hg • High flow oxygen therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure) • Mechanical ventilation or extracorporeal membrane oxygenation • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: <ul style="list-style-type: none"> ○ Acute respiratory distress syndrome ○ Acute renal failure ○ Acute hepatic failure ○ Acute right or left heart failure ○ Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg) ○ Acute stroke (ischemic or hemorrhagic) ○ Acute thrombotic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism ○ Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. ○ Admission to an intensive care unit ○ Death

Source: Study 301, version 9.0, dated May 14, 2021.

Abbreviations: COVID-19=coronavirus disease-2019; LRTI=lower respiratory tract infection

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