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

Identifying Information

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Review Completion Date	July 13, 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)
Intended Population	Individuals 18 years of age and older

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Glossary

AE	adverse event
AR	adverse reaction
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CMC	Chemistry, Manufacturing, and Control
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
MERS-CoV	Middle Eastern respiratory syndrome coronavirus
NVX-CoV2373	Novavax COVID-19 Vaccine, Adjuvanted
PIMMC	potential immune mediated medical condition
rS	recombinant spike protein
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VOC	variant of concern
VOI	variant of interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On February 1, 2022, FDA received a request from Novavax (the Sponsor) for emergency use authorization (EUA) of the Novavax COVID-19 Vaccine, Adjuvanted. The vaccine, also referred to as NVX-CoV2373, contains SARS-CoV-2 recombinant spike protein (SARS-CoV-2 rS) with Matrix-M adjuvant. The proposed use under an EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed primary series dosing regimen is two intramuscular injections at the dose level of 5 µg recombinant spike protein (rS) and 50 µg of Matrix-M adjuvant.

The EUA request includes safety and efficacy data from an ongoing multinational Phase 3 randomized, double-blind, placebo-controlled trial (study 301) and additional safety data from three additional studies. In study 301, approximately 30,000 adults ≥18 years of age were randomized 2:1 to receive NVX-CoV2373 (Novavax COVID-19 Vaccine, Adjuvanted) or placebo. The primary efficacy objective was to evaluate a 2-dose primary series of NVX-CoV2373 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second dose. 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"). The primary efficacy endpoint was assessed until a participant received the first blinded, crossover vaccination or until the data cutoff of September 27, 2021, whichever came first. During the period of collection of COVID-19 efficacy cases in early 2021, the B.1.1.7 (Alpha) variant was the predominant circulating COVID-19 strain. The per-protocol efficacy analysis population was defined as participants who were randomized, received both doses as assigned, had no evidence of SARS-CoV-2 infection prior to Dose 1, and did not have a COVID-19 event at any time before 7 days after the second injection.

As of September 27, 2021, the per-protocol efficacy analysis population included 17,272 NVX-CoV2373 recipients and 8,385 placebo recipients with a median of 2.5 months of follow-up post-Dose 2 during the blinded pre-crossover period. In the primary efficacy analysis in participants 18 years of age and older, vaccine efficacy (VE) against PCR-confirmed mild, moderate or severe COVID-19 was 90.4% (95% CI 83.8, 94.3). All COVID-19 cases in the NVX-CoV2373 arm were mild; in the placebo arm, 11% of cases were moderate and 5% were severe. In a subgroup analysis of VE by age, VE was 91.1% (95% CI 84.4, 94.9) in participants 18-64 years of age and 78.6% (95% CI -16.6, 96.1) in participants ≥65 years of age. The limited number of cases (n=6) in participants ≥65 years of age precluded a precise estimate of efficacy in this subgroup based on COVID-19 cases in the trial. Vaccine effectiveness in participants ≥65 years of age was further supported by a post-hoc immunogenicity analysis showing that SARS-CoV-2 neutralizing antibody titers in participants ≥65 years of age were comparable to those in participants 50-64 years of age (for whom the age subgroup-specific VE estimate was 90.7% [95% CI 72.9, 96.8]). Subgroup analyses of VE by risk for severe COVID-19, ethnicity and race were comparable to the per-protocol efficacy study population, except for VE in Hispanic/Latino participants (for whom the VE estimate was 77.0% [95% CI 48.7, 89.7]).

The safety analysis population included participants who received at least 1 dose of NVX-CoV2373 in the pre-crossover period (N=29,582; 19,735 NVX-CoV2373, 9,847 placebo) or post-crossover period (N=21,714; 6,416 NVX-CoV2373 crossover, 15,298 placebo crossover).

In the pre-crossover period, the median safety follow-up post-Dose 2 was 2.5 months; 77.6% of participants in the NVX-CoV2373 arm and 72.8% of participants in the placebo arm were followed for at least 2 months post-Dose 2. In the post-crossover period, the median safety follow-up post-Dose 4 was 4.4 months; 99% of participants in each treatment arm were followed for at least 2 months post-Dose 4. At FDA's request, the Sponsor provided additional safety data through an extraction date of February 17, 2022, for evaluation of clinically important adverse events. As of this later extraction date, the median post-crossover follow-up duration for participants in the Safety Analysis Set was 8.4 months after the completion of the 2-dose crossover series.

Solicited adverse reactions (ARs) were collected only in the pre-crossover period and were reported: by a higher proportion of NVX-CoV2373 recipients than placebo recipients, more frequently after NVX-CoV2373 Dose 2 than Dose 1 (local: 57.9% post-Dose 1, 78.7% post-Dose 2; systemic: 47.5% post-Dose 1, 69.3% post-Dose 2), and more frequently by younger adult (18-64 years) than older adult (≥65 year of age) NVX-CoV2373 recipients. In participants 18-64 years of age, the most common solicited ARs associated with any dose of NVX-CoV2373 in participants were injection site pain/tenderness (82.2%), fatigue (62.0%), headache (52.9%), and muscle pain (54.1%). In participants ≥65 years of age, the most common solicited ARs associated with any dose of NVX-CoV2373 in participants were injection site pain/tenderness (63.4%), fatigue (39.2%), headache (29.2%), and muscle pain (30.2%). Severe local and systemic ARs occurred in 1.2-7.2% and 2.4%-12.1% of NVX-CoV2373 recipients, respectively, and were more frequent after Dose 2 than after Dose 1. Most solicited reactions were mild to moderate and lasted 1-3 days.

In the pre-and post-crossover period, all unsolicited adverse events (AEs) and medically attended adverse events (MAAEs) were collected from Dose 1 through the 28 days post Dose 2 (participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo), and MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune mediated medical conditions [PIMMCs]) were collected for the duration of the study in all participants. In the blinded, placebo-controlled pre-crossover period, the proportions of participants reporting unsolicited AEs, MAAEs, and SAEs were comparable between the NVX-CoV2373 and placebo arms. Multiple events of myocarditis/ pericarditis were reported in temporal relationship to NVX-CoV2373 administration, similar to myocarditis following mRNA COVID-19 vaccines and raising concern for a causal relationship to NVX-CoV2373. Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX-CoV2373 arm, with the highest rate observed after Dose 2 (0.2%). Hypersensitivity reactions following NVX-CoV2373 were reported at a higher frequency (0.1%) than following placebo (0.03%). Review of the data also identified small imbalances in certain thromboembolic events, cholecystitis, uveitis, cardiac failure, and cardiomyopathy. However, a causal association between vaccination and these events cannot be concluded based on available data. Subgroup analyses of safety data did not reveal any notable differences across demographic groups. A review of additional safety data consisting of selected clinically important adverse events reported in three other clinical trials evaluating the NVX-CoV2373 vaccine manufactured at a different facility and by a different process identified an event of Guillain Barre syndrome and 2 additional cases of myocarditis/pericarditis with temporal relationship to vaccination and with no clear alternative etiology identified; otherwise, no other safety concerns were identified.

The 173rd meeting of the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) was held on June 7, 2022, to consider Novavax, Inc.'s EUA request for a vaccine to prevent COVID-19 in individuals 18 years of age and older. Following the presentations and committee discussion, the VRBPAC voted 21-0 (with 1 abstention) in favor of a determination that, based on the totality of scientific evidence available, the benefits of the Novavax COVID-19 Vaccine, Adjuvanted 2-dose series outweigh its risks for use in individuals 18 years of age and older.

Based on the totality of the scientific evidence available at this time to support the conclusion that the Novavax COVID-19 Vaccine, Adjuvanted may be effective, and that the known and potential benefits outweigh the known and potential risks associated with the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older, the review team recommends authorization of the Novavax COVID-19 Vaccine, Adjuvanted under EUA for use as a 2-dose series (5 µg SARS-CoV-2 rS antigen + 50 µg Matrix-M adjuvant per dose, 3 weeks apart) in individuals years of age 18 years of age and older. In anticipation of a future submission to support use of the Novavax COVID-19 Vaccine, Adjuvanted as a booster dose, the EUA Fact Sheets and Letter of Authorization will refer to the 2-dose series as a primary series.

2. SARS-CoV-2 Pandemic

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 respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death. For some adults, COVID-19 symptoms may continue for weeks to months after their initial illness (Chen et al, 2022).

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of May 26, 2022, has caused over 527 million cases of COVID-19, including 6.3 million deaths worldwide (WHO, 2022). In the US, approximately 83 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC, 2022a). From March 7, 2020, to May 14, 2022, adults 18 years of age and older accounted for 82.4% of COVID-19-associated hospitalizations and 99.8% of deaths from COVID-19 (CDC, 2022c).

Following emergency use authorization (EUA) of the first COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the US declined sharply during the first half of 2021. The emergence of the Omicron variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals were major factors in the resurgence of COVID-19 in the US. As of the week ending May 14, 2022, Omicron variant sub-lineages (predominantly BA.2 and BA2.12.1) comprised 98.8% of the tested strains in the US (CDC, 2022b).

3 Authorized and Approved Vaccines and Therapies for COVID-19

3.1 Comirnaty and Pfizer-BioNTech COVID-19 Vaccine

Comirnaty (COVID-19 Vaccine, mRNA) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid

particles. The vaccine is administered intramuscularly as two doses 3 weeks apart, with each 0.3 mL dose of the approved formulation containing 30 µg mRNA. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine, and the formulation authorized for use in individuals 12 years of age and older contains 30 µg mRNA in each 0.3 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 5-11 years of age contains 10 µg mRNA in each 0.2 mL dose. The Pfizer-BioNTech COVID-19 Vaccine formulation authorized for use in children 6 months through 4 years of age contains 3 µg mRNA in each 0.2 mL dose. During clinical development, the vaccine was called BNT162b2.

Comirnaty is approved as a 2-dose primary series for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine is authorized under EUA as: a 3-dose primary series for individuals 6 months through 4 years of age; a 2-dose primary series for individuals 5 years of age and older; a third primary series dose for individuals 5 years of age and older with certain immunocompromising conditions; a homologous first booster dose administered at least 5 months after completion of primary vaccination to individuals 5 years of age and older; a heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the dosing interval is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a second booster dose administered at least 4 months after a first booster dose with any FDA authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 12 years of age and older with certain immunocompromising conditions.

The Pfizer-BioNTech COVID-19 Vaccine safety and effectiveness data supporting approval of Comirnaty and emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.2 Spikevax and Moderna COVID-19 Vaccine

Spikevax, manufactured by Moderna, contains a nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles. The vaccine is approved for active immunization to prevent COVID-19 in individuals 18 years of age and older. The primary immunization series consists of 2 doses administered 1-month apart. The vaccine is authorized for emergency use (as the Moderna COVID-19 Vaccine) as: a 2-dose primary series for individuals 6 months of age and older; a third primary series dose for individuals 6 months of age and older with certain immunocompromising conditions; a homologous or heterologous first booster dose administered after completion of primary vaccination to individuals 18 years of age and older (the authorized dosing interval for a homologous booster is at least 5 months after completion of a primary series, and the authorized interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination); and a homologous or heterologous second booster dose administered at least 4 months after the first booster dose to individuals 50 years of age and older and individuals 18 years of age and older with certain immunocompromising conditions. Safety and effectiveness data supporting approval of Spikevax and authorization of Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

3.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine is authorized for use 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). Safety and effectiveness data supporting emergency use authorization of the Janssen COVID-19 Vaccine are detailed in the decision memorandum on the FDA website.

3.4 Therapies for COVID-19

The antiviral 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. Additionally, the immune modulator 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 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.

4. EUA Request for the Novavax COVID-19 Vaccine in Adults 18 Years of Age and Older

On February 1, 2022, FDA received Novavax, Inc.'s EUA request for authorization of Novavax COVID-19 Vaccine, Adjuvanted (also referred as NVX-CoV2373), to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The vaccine is constructed from the sequence of the full-length SARS-CoV-2 S protein of the prototype Wuhan-Hu-1 strain and codon-optimized for expression in baculovirus. The sequence was modified to express an rS protein that is resistant to protease cleavage at the S1/S2 site and stabilized in the prefusion conformation. The rS protein is produced by recombinant DNA technology using a baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species. The Matrix-M adjuvant is composed of Fraction-A and Fraction-C of saponin extracts from the soapbark tree, *Quillaja saponaria* Molina. The primary vaccination series consists of two doses (5 µg of SARS-CoV-2 rS protein with 50 µg Matrix-M adjuvant per dose, administered 3 weeks apart).

The primary source of clinical data to support the EUA request is from Study 2019nCoV-301, which provides safety, immunogenicity, and efficacy data from a total of approximately 30,000 adult participants (including from the United States) randomized 2:1 to receive 2 intramuscular injections of either NVX-CoV2373 (n=19,735) or placebo. NVX-CoV2373 vaccine drug product (DP) administered in this study was manufactured at Par Sterile Products, LLC. Available product and manufacturing information include a comprehensive analytical comparability assessment supporting quality comparability of the vaccine manufactured at Par Sterile Products, LLC (used in Study 301) to the vaccine product intended for use under EUA.

Additional safety data from a total of 10,323 additional NVX-CoV2373 recipients are provided from international studies (2019nCoV-302, 2019nCoV-501, 2019nCoV-101) with vaccine produced by an earlier manufacturing process than the vaccine product evaluated in study 301. The vaccine product lots used in these three studies were manufactured at Emergent BioSolutions. Due to differences in manufacturing process and product testing, FDA could not conclude that vaccine lots manufactured at Emergent BioSolutions are comparable to those manufactured at Par Sterile Products, LLC, and available manufacturing and product information will not allow for a conclusion of comparability between vaccine manufactured at Emergent BioSolutions and vaccine intended for use under EUA. Therefore, efficacy and immunogenicity data from these three other studies are not considered supportive of the EUA request and are not discussed in this memo.

5. EUA Requirements, Guidance, and Considerations Pertaining to COVID-19 Vaccines

5.1 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.

5.2 Regulatory Considerations for EUA for COVID-19 Vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry Emergency Use Authorization for Vaccines to Prevent COVID-19 originally issued October 2020 and last updated March 2022).

Effectiveness Data

Data adequate to inform an assessment of the vaccine's benefits and risks, and thus support issuance of an EUA, would include meeting the prespecified success criteria for the study's primary efficacy endpoint (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).

Safety Data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3

trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-Up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt. From the perspective of vaccine efficacy, a 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

6. FDA Review of Clinical Safety and Effectiveness Data

6.1 Overview of Clinical Studies

The EUA request included data from four ongoing clinical studies summarized in Table 1. As discussed in Section 4 above, due to differences in manufacturing process between the vaccine lots used in the studies and the vaccine product intended for use under EUA, the primary source of clinical evidence to support safety and efficacy of NVX-CoV2373 is study 2019nCoV-301. Efficacy and immunogenicity data from the other studies is not included in this review, and safety data from these studies was reviewed as relevant information to further inform the safety of the vaccine product intended for use under EUA.

Table 1. Clinical Trial Overview: Data Considered in Support of Safety and Effectiveness of Novavax COVID-19 Vaccine Primary Series in Adults 18 Years and Older

Study Number/ Country	Description	NVX-CoV2373[1] Number[2]	Vaccine Manufacturing Site[3]	Comparator Number[2]	Study Status
Main study	--	--	--	--	--
2019nCoV-301 USA, Mexico (Study 301)	Phase 3, randomized, observer-blinded, placebo-controlled study to evaluate the safety, efficacy, and immunogenicity of NVX-CoV2373 vaccine	19735	Par Sterile Products, LLC	9847	Ongoing

Study Number/ Country	Description	NVX-CoV2373[1] Number[2]	Vaccine Manufacturing Site[3]	Comparator Number[2]	Study Status
Supporting studies (safety)	--	--	--	--	--
2019nCoV-302 United Kingdom (Study 302)	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study to evaluate safety, efficacy, and immunogenicity of NVX-CoV2373 vaccine	7570	Emergent BioSolutions	7564	Ongoing
2019nCoV-501 South Africa (Study 501)	Phase 2, randomized, observer-blinded, placebo-controlled in healthy HIV-negative adults ≥18 to ≤84 years of age and in medically stable HIV-positive adults ≥18 to ≤64 years of age.	2211	Emergent BioSolutions	2197	Ongoing
2019nCoV-101, Part 1 Australia (Study 101 pt1)	Phase 1, randomized, observer-blinded, placebo-controlled in healthy adults ≥18 to ≤59 years of age	29	Emergent BioSolutions	23	Completed
2019nCoV-101, Part 2 Australia USA (Study 101 pt2)	Phase 2, randomized, observer-blinded, placebo-controlled in adults ≥18 to ≤84 years of age	514	Emergent BioSolutions	255	Ongoing

Source: adapted from EUA 28237, amendment 0, page 35, Table 10.
Abbreviations: COVID-19=coronavirus disease-2019; HIV=human immunodeficiency virus; rS=recombinant spike protein; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
1. 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant.
2. Number is the total number of participants in the Safety Analysis Set in the pre-crossover period.
3. Pre-crossover period (from randomization to the time of cross-over): NVX-CoV2373 vaccine was manufactured at Par Sterile Products, LLC (study 301) and at Emergent BioSolutions (studies 302, -502, and -101). Blinded cross-over period (cross-over to the time of data cutoff): NVX-CoV2373 vaccine was manufactured at Par Sterile Products, LLC (studies 301, -302, and 501). There was no blinded cross-over period in study 101.
Cutoff Dates: Study 101: December 19, 2020 (part 1) and December 15, 2020 (part 2), Study 501: February 23,2021, Study 302: February 23, 2021, Study 301: September 27. 2021.

6.2 Study 2019nCoV-301

6.2.1 Design

Study 2019nCoV-301 (referred to as Study 301) is an ongoing randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of NVX-CoV2373

in adults ≥18 years of age. The study is being conducted at 119 sites in the US and Mexico. Study 301 also included an adolescent primary series expansion substudy and a booster dose substudy; however, with the exception of several adverse events reported in these substudies, this memo includes only the study design and pertinent VE, safety and immunogenicity analyses of the primary series in adults.

The study was initiated on December 27, 2020 (first participant screened) and completed enrollment on February 18, 2021. Participants are being followed for up to 24 months after the second dose for safety and efficacy assessments.

A total of 29,945 participants were randomized 2:1 to receive 2 intramuscular injections (Dose 1 and Dose 2) of either NVX-CoV2373 (containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) or saline placebo, administered 21 days apart, at Day 0 and Day 21 (vaccination window of up to +7 days). Participants were stratified by age group (18 to ≤64 years of age and ≥65 years of age). A target enrollment of 25% of the study population was to consist of participants ≥65 years of age. Prioritization for enrollment was to be given to individuals at high risk for COVID-19 by virtue of Black/African American or Native American race, Hispanic/Latino ethnicity, co-morbid conditions (e.g., obesity [BMI >30 kg/m^2], chronic kidney or lung disease, cardiovascular disease, or diabetes mellitus type 2), and life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [e.g., factory or meat packing plants, essential retail workers, etc.]). Eligible participants included subjects with clinically stable chronic conditions (such as well-controlled HIV infection) who had no previous history of laboratory confirmed SARS-CoV-2 infection or COVID-19 prior to randomization. The study excluded participants with immunodeficiency conditions, those who received immunosuppressive therapy, or immunoglobulin or blood derived products within 90 days, were pregnant or breastfeeding, or had a history of laboratory-confirmed COVID-19.

In response to evolving public health recommendations for and availability of COVID-19 vaccines authorized for EUA, the Sponsor modified the study plan after the EUA-required safety data had been accrued (median duration of 2 months safety follow-up after the second vaccination) to offer crossover from the originally assigned study treatment to the other study treatment (vaccine or placebo) in a blinded fashion (Dose 3 and Dose 4 “blinded crossover”). The Sponsor has communicated plans for future analyses of efficacy after the blinded crossover period to evaluate efficacy of according to time since vaccination (comparing COVID-19 cases in pre- vs. post-crossover vaccine recipients), though these analyses have not been submitted for FDA review.

The primary efficacy objective was to evaluate a 2-dose primary series regimen of NVX-CoV2373 compared to placebo against polymerase chain reaction (PCR)-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination in participants ≥18 years of age. Efficacy was assessed through daily surveillance of symptoms suggestive of COVID-19 throughout the study follow-up. Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. Additionally, subjects are given an at-home test to use for 3 days (3-Day Self-Collection Kit). For the diagnosis of SARS-CoV-2 infection, FDA-authorized PCR tests were used, irrespective whether the test was performed by participant with 3-Day Self-Collection Kit or at study sites, and swabs are sent to a central laboratory. Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase

chain reaction [RT-PCR] assay) by the central laboratory was required to meet the primary and secondary efficacy endpoint case definitions.

The primary efficacy endpoint was assessed with data collected up to the blinded crossover period or through September 27, 2021. Participants who were unblinded with an intention to receive a COVID-19 vaccine under EUA were censored past the time of unblinding.

The study will remain blinded at the participant level for study site personnel and study participants until the end of the study (24 months after the first vaccination) while the Sponsor was unblinded at the participant level to prepare for regulatory submissions. An unblinded statistician and programmer prepared data analyses.

Case Definitions

The COVID-19 case definitions for mild, moderate, and severe Covid-19 are summarized in Table 2.

Table 2. COVID-19 Case Definitions

Severity	Case Definition
Mild	• 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	• 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:
	  ○ Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline)
	  ○ Tachypnea: 24 to 29 breaths per minute at rest
	  ○ SpO_2: 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)

Severity	Case Definition
Severe	• 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: o Acute respiratory distress syndrome o Acute renal failure o Acute hepatic failure o Acute right or left heart failure o Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg) o Acute stroke (ischemic or hemorrhagic) o Acute thrombotic event: acute myocardial infarction, deep vein thrombosis, pulmonary embolism o Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. o Admission to an intensive care unit o Death

Source: Study 301, version 9.0, dated May 14, 2021.
Abbreviations: COVID-19=coronavirus disease-2019; LRTI=lower respiratory tract infection

All cases meeting the severe/critical criteria were adjudicated by a blinded clinical severity adjudication committee to determine if the case was severe/critical in their judgement.

Primary Efficacy Endpoint and Statistical Criteria

- The primary endpoint was first episode of PCR-positive mild, moderate, or severe COVID-19.
  - The relative risk (RR) of incidence rates was estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance. To assess incident rates rather than absolute counts of cases accounting for differences in follow-up times among participants, an offset was utilized in the Poisson regression. A 2-sided 95% CI was constructed around the estimate.
  - The statistical success criteria for the primary endpoint were evaluated with a 2-sided 0.05 α hypothesis test for the following hypothesis:
    H1: VE ≥50% efficacy AND lower bound of 95% CI >30% (RR ≤70%), where Vaccine Efficacy% = [1-Relative Risk] x 100

Selected Secondary Efficacy Objectives/Endpoints

To assess:

- First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a “variant of concern / interest” according to the CDC Variants Classification.

- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint and efficacy
- VE against any symptomatic SARS-CoV-2 infection
- VE according to race and ethnicity
- VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ⩾65 years with or without co-morbidities or age <65 years with co-morbidities (e.g., obesity [body mass index (BMI) >30 kg/m^2], chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (e.g., factory or meat packing plants, essential retail workers, etc.)]).

Exploratory Endpoint

To evaluate the efficacy of study vaccine compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant considered as a "variant of concern / interest" according to the CDC Variants Classification, diagnosed ≥7 days after completion of the second vaccination in the initial set of vaccinations of adult participants ≥18 years of age

Evaluation of Safety

Safety follow-up evaluations are planned through 24 months post-last dose of the primary series.

Safety assessments included the following:

- Solicited local and systemic adverse reactions (ARs) during the 7 days following vaccination, pre-crossover (also described as reactogenicity symptoms)
- Unsolicited adverse events (AEs), both pre- and post-crossover, from Dose 1 through the 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo
- Medically attended AEs (MAAEs), both pre- and post-crossover, from Dose 1 through the 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo or if only Dose 1 is provided then 49 days after Dose 1 i
- MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and PIMMCs), both pre- and post-crossover, for the duration of the study in all participants
- Vital sign measurements at specified clinic visits in all participants
- Physical examination findings at specified clinic visits in all participants
- Pregnancy and accompanying outcomes in all participants

The Data Safety Monitoring Committee, consisting of external experts, monitored safety and advised the Sponsor at scheduled and *ad hoc* meetings. An unblinded statistician monitored

data for the pre-specified stopping boundary, which would indicate that the vaccine causes harm by increasing the rate of mild, moderate or severe COVID-19.

Datasets Reviewed

The Sponsor submitted cleaned and validated safety and efficacy data for independent FDA analysis through September 27, 2021 (cutoff date), and additional safety data as requested by FDA through a February 17, 2022, extraction date for assessment of clinically important safety events (e.g., SAEs, AESIs) collected after the September 27, 2021 data cutoff date. These additional safety data had not been cleaned up to the later extraction date.

Evaluation of Immunogenicity

Assessment of humoral antibody responses to SARS-CoV-2 protein was included as a secondary study objective. Blood samples were collected at Days 0, 21, and 35 from approximately 1,200 participants randomly selected by biostatisticians who were blinded to the vaccine assignment. The random selection included approximately 600 participants from each age cohort (18-64 years, 65 years and older), each of which included approximately 400 NVX-CoV2373 recipients and 200 placebo recipients.

Analysis Populations

The definition of each analysis population is included in Table 3.

Table 3. Analysis Sets

Population	Description
Full Analysis Set (FAS)	Participants who were randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data.
Per-Protocol Efficacy	Participants who were randomized, received both doses as assigned, had no immunologic or virologic evidence of prior COVID-19 at the time of vaccination, and no major protocol deviations that would impact the efficacy outcomes (e.g., baseline seropositivity for anti-SARS-CoV-2 nucleoprotein, baseline positivity for SARS-CoV-2 RNA RT-PCR from nasal swab, COVID-19 event at any time before 7 days after the second injection, participants were censored at the time of protocol deviation).
Per-Protocol Efficacy Set 2	Participants meeting criteria for inclusion in the Per-Protocol Efficacy Set, with the exception that participants with baseline seropositive status are not excluded (to allow for evaluation of the impact of baseline seropositivity or virological positivity on vaccine efficacy).
Per-Protocol Immunogenicity	Participants that have at least a baseline and 1 serum sample result available after vaccination and have no major protocol violations that would impact immunological measures at the specified timepoint.
Safety	Participants who were randomized and received at least 1 dose of study vaccine/placebo. For participants who received both active and placebo vaccine during the initial or crossover period, the participant was analyzed as part of the active group.

Source: Study 301 protocol version 9.0, dated May 14, 2021.
Abbreviations: SARS-CoV-2=severe acute respiratory syndrome coronavirus; RT-PCR=reverse transcription polymerase chain reaction; COVID-19=coronavirus disease-2019.

At the time of the data cutoff date of September 27, 2021, the median pre-crossover follow-up duration for participants in the Safety Analysis Set was 2.5 months after the completion of primary series (Dose 2). At the time of the data cutoff date of February 17, 2022, the median

post-crossover follow-up duration for participants in the Safety Analysis Set was 8.4 months after the completion of the crossover series (Dose 4).

6.2.2 Participant Disposition and Inclusion in Analysis Populations

Table 4 describes the disposition of participants among all randomized participants (data cut off September 27, 2021). A larger percentage of participants in the placebo arm discontinued during the pre-crossover period (22.2% in the placebo group versus 12.2% in the vaccine group). A major reason for discontinuation is withdrawal by subject (16.3% in the placebo arm versus 7.9% in the vaccine arm). Table 5 describes the analysis populations and the reasons for exclusion from each (data cut off September 27, 2021). The proportion of participants excluded from the Per-Protocol Efficacy Set was balanced between treatment arms, with the majority excluded due to positive baseline SARS-CoV-2 status (either positive anti-NP or PCR result). Other participants were excluded because they did not complete the vaccine schedule or were censored prior to the observation period (7 days post dose 2). In the Per-Protocol Efficacy Set, during the pre-crossover period, 21.7% of the participants who received placebo were additionally unblinded with the intention to receive a COVID-19 vaccine under EUA as compared to 13.2% of the participants who received NVX-CoV2373. Participants who were unblinded to receive a COVID-19 vaccine under EUA were censored in the efficacy analyses at the time of unblinding. In the Per-Protocol Efficacy Set, 78.0% of vaccine recipients and 73.1% of placebo recipients completed at least 2 months of pre-crossover follow-up after Dose 2. This difference in follow-up may be the result of more placebo recipients being censored at the time of unblinding to receive a COVID-19 vaccine under EUA. Table 4 summarizes the disposition of all participants as randomized. Some differences may be observed in percentages of unblinded participants and those who withdrew from the study when other analysis populations are used.

Table 4. Disposition, All Randomized Participants, Study 301, September 27, 2021 Cutoff

Disposition	NVX-CoV2373 N=19963	Placebo N=9882	Total N=29945
Randomized, n (%)	19963	9982	29945
Treated, n (%)	19714 (100)	9868 (100)	29582 (100)
Blinded, placebo-controlled follow-up period, n (%)	--	--	--
Completed 1 dose	19714 (100)	9868 (100)	29582 (100)
Completed 2 doses	19087 (96.8)	9440 (95.7)	28527 (96.4)
Discontinued from original blinded vaccination period	2407 (12.2)	2192 (22.2)	4599 (15.5)
Reason for discontinuation	--	--	--
Withdrawal by subject	1563 (7.9)	1604 (16.3)	3167 (10.7)
Lost to follow up	741 (3.8)	501 (5.1)	1242 (4.2)
Other	74 (0.4)	75 (0.8)	149 (0.5)
Adverse event	18 (<0.1)	6 (<0.1)	24 (<0.1)
Death	11 (<0.1)	6 (<0.1)	17 (<0.1)

Disposition	NVX-CoV2373 N=19963	Placebo N=9882	Total N=29945
Blinded crossover period, n (%)	--	--	--
Did not receive NVX-CoV2373 or placebo	4395 (22.3)	3473 (35.2)	7868 (26.6)
Crossed over to receive NVX-CoV2373 or placebo	15319 (77.7)	6395 (64.8)	21714 (73.4)
Completed dose 3	15319 (77.7)	6395 (64.8)	21714 (73.4)
Completed dose 4	15103 (76.6)	6327 (64.1)	21431 (72.4)
Discontinued prior to dose 3	0	0	0
Discontinued after dose 3 but before dose 4	175 (0.9)	56 (0.6)	231 (0.8)
Discontinued after dose 4	491 (2.5)	138 (1.4)	629 (2.1)
Discontinued from blinded crossover vaccine period	666 (3.4)	194 (2.0)	860 (2.9)
Reason for discontinuation	--	--	--
Withdrawal by subject	433 (2.2)	104 (1.1)	537 (1.8)
Lost to follow up	185 (0.9)	74 (0.7)	259 (0.9)
Other	24 (0.1)	4 ((<0.1)	28 ((<0.1)
Adverse event	1 (<0.1)	2 (<0.1)	3 (<0.1)
Death	23 (0.1)	10 (0.1)	33 (0.1)

Source: EUA 28237 Amendment 24, Clinical Summary for Clinical Study 2019nCoV-301, Table 1.
Data cutoff September 27, 2021
n=number of participants with indicated disposition. Denominators for percentages are the number of treated participants.
N= number of randomized participants.

Table 5. Disposition, Efficacy Analysis Population, Study 301

Disposition	NVX-CoV2373	Placebo	Total
ITT Set[1,2], N	19963	9982	29945
Excluded from all analysis sets, n (%)	--	--	363
Sponsor exclusion[3]	--	--	289
Not dosed	--	--	74
FAS Set[4,5], n (%)	19714 (98.8)	9868 (98.9)	29582 (98.8)
PP-EFF[4,5], n (%)	17272 (87.6)	8385 (85.0)	25657 (86.7)
Excluded from PP-EFF	2442 (12.4)	1483 (15.0)	3925 (13.3)
Reason for exclusion	--	--	--
Baseline positive anti-NP result	1100 (5.6)	622 (6.3)	1722 (5.8)
Censored prior to observation period	652 (3.3)	405 (4.1)	1057 (3.6)
Unblinded	339 (1.7)	194 (2.0)	533 (1.8)
Protocol deviation	173 (0.9)	170 (1.7)	343 (1.2)
Post-baseline positive PCR result	109 (0.6)	70 (0.7)	179 (0.6)
Withdrawal from Study	104 (0.5)	76 (0.8)	180 (0.6)
Death	0	1 (<0.1)	1 (<0.1)
Did not complete vaccination schedule	627 (3.2)	428 (4.3)	1055 (3.6)
Baseline positive PCR result	228 (1.2)	109 (1.1)	337 (1.1)

Disposition	NVX-CoV2373	Placebo	Total
PP-EFF-2[6,7], n (%)	18438 (93.5)	9035 (91.6)	27473 (92.9)
Excluded from PP-EFF-2[8]	1276 (6.5)	833 (8.4)	2109 (7.1)
Reason for exclusion	--	--	--
Censored prior to observation period	652 (3.3)	405 (4.1)	1057 (3.6)
Unblinded	339 (1.7)	194 (2.0)	533 (1.8)
Protocol deviation[9]	173 (0.9)	170 (1.7)	343 (1.2)
Post-baseline positive PCR result	109 (0.6)	70 (0.7)	179 (0.6)
Withdrawal from study	104 (0.5)	76 (0.8)	180 (0.6)
Death	0	1 (<0.1)	1 (<0.1)
Did not complete vaccination schedule	627 (3.2)	428 (4.3)	1055 (3.6)

Source: EUA 28237, Amendment 26. Response-request28.pdf, Table 4, page 3.
Abbreviations: FAS=Full Analysis Set; ITT=intent-to-treat; N=number of subjects in indicated analysis set; n=number of subjects with indicated disposition; NP-nucleocapsid protein; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy Set
1. Intent-to Treat: all participants randomized into the study.
2. Percentages were calculated based on randomized participants.
3. Sponsor exclusion included all participants excluded from Site US151 due to source data inadequate to verify clinical data and other Good Clinical Practice violations, and some participants excluded from Site US076 that received a second dose between February 5, 2021, and February 12, 2021, using an incorrect lot number.
4. FAS: all participants randomized who received at least 1 dose of study vaccine/placebo and tabulated with randomized treatment.
5. Percentages were calculated based on randomized (ITT Analysis Set) in each column.
6. PP-EFF Analysis Set: all participants who received the full prescribed regimen of study vaccine/ placebo, had no major protocol deviations prior to first COVID-19 positive episode or administrative censoring, with no confirmed infection or prior infection due to SARS-CoV-2 at baseline and not censored prior to the start of the observation period.
7. Percentages were calculated based on the FAS in each column.
8. PP-EFF-2 Analysis Set followed the same method described in the PP-EFF Analysis Set except that it included all participants regardless of baseline SARS-CoV-2 serostatus.
9. Includes additional protocol deviations that did not result in censoring prior to observation period.
Note: Participants may be excluded for more than 1 reason.

A total of 289 participants from 2 sites were excluded from safety and efficacy populations. Participants from Site 151 were excluded due to inadequate source data and ability to verify the Principal Investigator's compliance with the following regulations: 21 CFR 312.60: General Responsibilities of Investigators, 21 CFR 312.62(b): Investigator recordkeeping and record retention – Case histories, and 21 CFR 312.64(b): Investigator Reports – Safety Reports. Some participants from Site 76 were excluded because of vaccine administration errors, including administration of vaccine using an incorrect lot number.

6.2.3 Demographics and Other Baseline Characteristics

Table 6 and Table 7 describe the demographics and other baseline characteristics of participants included in the Safety Analysis Set and the Per-Protocol Efficacy set.

Table 6. Demographics and Other Baseline Characteristics, Safety Analysis Set, Study 301

Characteristic	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29945
Sex, n (%)	--	--	--
Male	10367 (52.5)	5019 (51.0)	15386 (52.0)
Female	9368 (47.5)	4828 (49.0)	14196 (48.0)
Age (years)	--	--	--
Mean (SD)	46.5 (15.05)	46.8 (14.95)	46.6 (15.02)
Median	47.0	47.0	47.0
Minimum, maximum	18, 95	18, 90	18, 95
Age subgroups, n (%)	--	--	--
18 to <65 years	17255 (87.4)	8612 (87.5)	25867 (87.4)
≥65 years	2480 (12.6)	1235 (12.5)	3715 (12.6)

Characteristic	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29945
Race, n (%)	--	--	--
White	14794 (75.0)	7381 (75.0)	22175 (75.0)
Black or African American	2323 (11.8)	1164 (11.8)	3487 (11.8)
American Indian or Alaska Native[1]	1309 (6.6)	661 (6.7)	1970 (6.7)
Asian	810 (4.1)	416 (4.2)	1226 (4.1)
Multiple	325 (1.6)	159 (1.6)	484 (1.6)
Native Hawaiian or Other Pacific Islander	56 (0.3)	12 (0.1)	68 (0.2)
Not reported	110 (0.6)	47 (0.5)	157 (0.5)
Missing	8 (<0.1)	7 (<0.1)	15 (<0.1)
Ethnicity, n (%)	--	--	--
Not Hispanic/Latino	15345 (77.8)	7669 (77.9)	23014 (77.8)
Hispanic/Latino	4334 (22.0)	2155 (21.9)	6489 (21.9)
Not reported	32 (0.2)	19 (0.2)	51 (0.2)
Missing or unknown	24 (0.1)	4 (<0.1)	28 (<0.1)
Country, n (%)	--	--	--
Mexico	1176 (6.0)	588 (6.0)	1764 (6.0)
United States	18559 (94.0)	9259 (94.0)	27818 (94.0)
Occupational risk, n (%)	--	--	--
Work requires close proximity to others	7796 (39.5)	3798 (38.6)	11594 (39.2)
Comorbidities, n (%)	--	--	--
Obesity (BMI >30 kg/m^2)	7289 (36.9)	3668 (37.2)	10957 (37.0)
Chronic kidney disease	149 (0.8)	64 (0.6)	213 (0.7)
Chronic lung disease	2776 (14.1)	1446 (14.7)	4222 (14.3)
Cardiovascular disease	226 (1.1)	126 (1.3)	352 (1.2)
Diabetes mellitus type 2	1525 (7.7)	814 (8.3)	2339 (7.9)
High-risk adults[2], n (%)	--	--	--
Yes	18811 (95.3)	9378 (95.2)	28189 (95.3)
No	924 (4.7)	469 (4.8)	1393 (4.7)
Baseline SARS-CoV-2 status (anti-NP or PCR)	--	--	--
Negative	18462 (93.5)	9156 (93.0)	27618 (93.4)
Positive	1273 (6.5)	691 (7.0)	1964 (6.6)

Source: EUA 28237 Amendment 24, Table 19.
N=number of participants in cohort; n=number of participants with indicated characteristic.
Abbreviations: BMI=body mass index; NP=nucleocapsid protein; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus; SD=standard deviation
1. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were enrolled at sites in the United States.
2. High-risk adults were 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; 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.

Table 7. Demographics and Other Baseline Characteristics, Per-Protocol Efficacy Set, Study 301

Characteristic	NVX-CoV2373 N=17272	Placebo N=8385	Total N=25657
Sex, n (%)	--	--	--
Male	8989 (52.0)	4227 (50.4)	13216 (51.5)
Female	8283 (48.0)	4158 (49.6)	12441 (48.5)
Age (years)	--	--	--
Mean (SD)	46.3 (14.90)	46.7 (14.74)	46.4 (14.85)
Median	47.0	47.0	47.0
Minimum, maximum	18, 95	18, 90	18, 95

Characteristic	NVX-CoV2373 N=17272	Placebo N=8385	Total N=25657
Age subgroups, n (%)	--	--	--
18 to <65 years	15228 (88.2)	7417 (88.5)	22645 (88.3)
≥65 years	2044 (11.8)	968 (11.5)	3012 (11.7)
Race, n (%)	--	--	--
White	13124 (76.0)	6350 (75.7)	19474 (75.9)
Black or African American	1881 (10.9)	947 (11.3)	2828 (11.0)
American Indian or Alaska Native[1]	1068 (6.2)	522 (6.2)	1590 (6.2)
Asian	757 (4.4)	375 (4.5)	1132 (4.4)
Multiple	296 (1.7)	137 (1.6)	433 (1.7)
Native Hawaiian or Other Pacific Islander	47 (0.3)	10 (0.1)	57 (0.2)
Not reported	92 (0.5)	39 (0.5)	131 (0.5)
Missing	7 (<0.1)	5 (<0.1)	12 (<0.1)
Ethnicity, n (%)	--	--	--
Not Hispanic/ Latino	13526 (78.3)	6572 (78.4)	20098 (78.3)
Hispanic/Latino	3707 (21.5)	1801 (21.5)	5508 (21.5)
Not reported	21 (0.1)	10 (0.1)	31 (0.1)
Missing or unknown	18 (0.1)	2 (<0.1)	20 (<0.1)
Country, n (%)	--	--	--
Mexico	1011 (5.9)	498 (5.9)	1509 (5.9)
United States	16261 (94.1)	7887 (94.1)	24148 (94.1)
Occupational risk, n (%)	--	--	--
Work requires close proximity to others	6787 (39.3)	3177 (37.9)	9964 (38.8)
Comorbidities, n (%)	--	--	--
Obesity (BMI >30 kg/m^2)	6344 (36.7)	3157 (37.7)	9501 (37.0)
Chronic kidney disease	125 (0.7)	56 (0.7)	181 (0.7)
Chronic lung disease	2461 (14.2)	1264 (15.1)	3725 (14.5)
Cardiovascular disease	199 (1.2)	101 (1.2)	300 (1.2)
Diabetes mellitus type 2	1308 (7.6)	698 (8.3)	2006 (7.8)
High-risk adults[2], n (%)	--	--	--
Yes	16455 (95.3)	7972 (95.1)	24427 (95.2)
No	817 (4.7)	413 (4.9)	1230 (4.8)

Source: EUA 28237 Amendment 24, Table 4.

Abbreviations: BMI=body mass index; eCRF=electronic case report form; N=number of participants in cohort; n=number of participants with indicated characteristic; NP=nucleocapsid protein; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus; SD=standard deviation

1. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were enrolled at sites in the United States.

2. High-risk adults were 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; 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.

In the Per-Protocol Efficacy Set and the Safety Analysis Set, participants in the NVX-CoV2373 and placebo arms were similar with respect to demographic and baseline characteristics. There were no significant imbalances in demographic or other baseline characteristics between the Safety Analysis Set and Per-Protocol Efficacy Set. Overall, 6.5% of NVX-CoV2373 vaccine recipients and 8.4% of placebo recipients had evidence of previous infection with SARS-CoV-2 at baseline, as assessed by serology prior to vaccination. Participants in the Safety Analysis Set were enrolled from 119 sites in 2 countries (US and Mexico). The post-crossover demographic and baseline characteristics for the Safety Analysis Set were generally similar to the pre-crossover set.

6.2.4 Vaccine Efficacy

6.2.4.1 Primary Efficacy Analysis

The primary endpoint was the first episode of PCR-confirmed mild, moderate, or severe COVID-19. The analysis was based on the Per-Protocol Efficacy Set.

A total of 96 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination accrued for the September 27, 2021, updated analysis of the primary efficacy endpoint (Table 8). Of the 96 cases, 17 occurred in the NVX-CoV2373 arm and 79 occurred in the placebo arm. All 17 cases of COVID-19 in the NVX-CoV2373 arm were mild in severity. Of the 79 COVID-19 cases in the placebo arm, 66 were mild (84%), 9 were moderate (11%), and 4 cases were severe (5%). There were no hospitalizations or deaths due to COVID-19 among the 96 primary endpoint COVID-19 cases in this study. One fatal case of COVID-19 was reported in a placebo recipient who received another COVID-19 vaccine (available under EUA) prior to the event; therefore, this was not included as a primary endpoint COVID-19 case.

As shown in Table 8, VE against mild to severe COVID-19 with onset at least 7 days after the second dose was 90.4% (95% CI 83.8, 94.3), which met the pre-specified statistical success criteria (50% efficacy AND lower bound of 95% CI >30%) for the primary analysis of efficacy. In subgroup analyses by age, VE in participants 18 to <65 years of age was comparable to overall VE; however, for participants ≥65 years of age, the VE was lower at 78.6%, with wide 95% confidence intervals.

Table 8. Vaccine Efficacy in Protecting Against PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From 7 Days After Second Injection, Per-Protocol Efficacy Set, Study 301

Age Group	NVX-CoV2373 Cases[1] n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Placebo Cases[1] n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Vaccine Efficacy[2] (95% CI)
All participants	17/17272 (0.098) (5.59)[3]	79/8385 (0.942) (58.30)[3]	90.41 (83.81, 94.32)
18 to <65 years	15/15228 (0.099) (5.70)	75/7417 (1.011) (63.69)	91.06 (84.44, 94.87)
≥65 years	2/2044 (0.098) (5.76)	4/968 (0.413) (26.52)	78.63 (-16.64, 96.08)

Source: EUA 28237 Amendment 53, Table 7
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=ratio of incidence rates.
N=number of participants in cohort; n=number of cases[1]
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE(%) =100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (September 27, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive.
Note: RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and age strata as fixed effects and robust error variance (Zou, 2004) fitted for all participants.
3. Mean incidence rate was estimated with weighting for age strata (18 to <65 years of age or ≥65 years of age) reflective of the distribution seen in the study population.

An additional supportive analysis of the primary efficacy endpoint by baseline SARS-CoV-2 status was performed using the PP-EFF-2 Analysis Set. Among the 300 participants with positive baseline SARS-CoV-2 as determined by PCR (n=204 in the NVX-CoV2373 arm and n=96 in the placebo arm) there were no COVID-19 cases that occurred at least 7 days after Dose 2. The VE, regardless of baseline SARS-CoV-2 status, was 89.8% (95% CI 83.0, 93.9).

Vaccine Efficacy by Age

The limited number of cases (n=6) in participants ≥65 years of age precluded a conclusive assessment of efficacy in this subgroup, with very wide confidence intervals noted. To provide supportive data for effectiveness in the elderly population, neutralizing antibody titers in participants 50-64 years of age were compared descriptively to those in participants ≥65 years of age, and a post-hoc analysis of VE among participants 50-64 years of age was conducted at FDA's request. In the subgroup of participants 50-64 years of age, primary endpoint cases were reported by 4 participants in the NVX-CoV2373 arm, and 20 participants in the placebo arm, resulting in VE (90.7% [95% CI 72.9, 96.8]) that was comparable to the overall VE for ages 18 years and older (90.4% [95% CI 83.8, 94.3]) and for ages 18-64 years (91.1% [95% CI 84.4, 94.9]).

Table 9 summarizes the results of the immunogenicity comparison between the age groups, showing that the Day 35 neutralizing antibody GMT was slightly lower for participants 65 years of age and older compared with participants 50-64 years of age, with a GMT ratio ($GMT_{\geq 65\ Years}/GMT_{50\text{-}64\ Years}$) of 0.91 and a lower bound of the associated 95% CI that would have met FDA's usual immunobridging success criterion for non-inferiority (>0.67).

Table 9. SARS-CoV-2 Neutralizing GMTs at Baseline (Day 0) and 14 Days After Second Vaccination in Participants 50-64 Years of Age, Per Protocol Immunogenicity Analysis Set, Study 301

Timepoint	NVX-CoV2373 Participants 50-64 Years N=144	NVX-CoV2373 Participants ≥65 Years N=358	GMR
Day 0 (baseline)	--	--	--
GMT	10.2	10.4	--
95% CI	9.8, 10.7	10.0, 10.9	--
Day 35	--	--	--
GMT	978.6	899.8	--
95% CI	770.5, 1243.0	762.9, 1061.3	--
GMR ($GMT_{\geq 65\ Years}/GMT_{50\text{-}64\ Years}$)	--	--	0.91
95% CI	--	--	0.68, 1.2

Source: adapted from EUA 28237, amendment 32, t_imm_50to64_and65_updated.docx.
Abbreviations: CI=confidence interval; GMR=geometric mean ratio; GMT=geometric mean titer; MN=microneutralization assay, SARS-CoV-2 strain: Wuhan-Hu-1.
N=number of SARS-CoV2 baseline seronegative 50-64 and ≥65-year-olds. Baseline defined as the last non-missing assessment prior to the study vaccine administration.

6.2.4.2 Secondary Efficacy Analyses

PCR-Confirmed COVID-19 Cases Any Time After the First or Second Dose

A supportive analysis of PCR-confirmed COVID-19 cases any time after the first or second dose and any time after Dose 1 and before Dose 2 was performed using the Full Analysis Set. A total of 289 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 occurred with onset from first vaccination, including 133 participants in the NVX-CoV2373 arm and 156 participants in the placebo arm. This analysis is presented in Table 10.

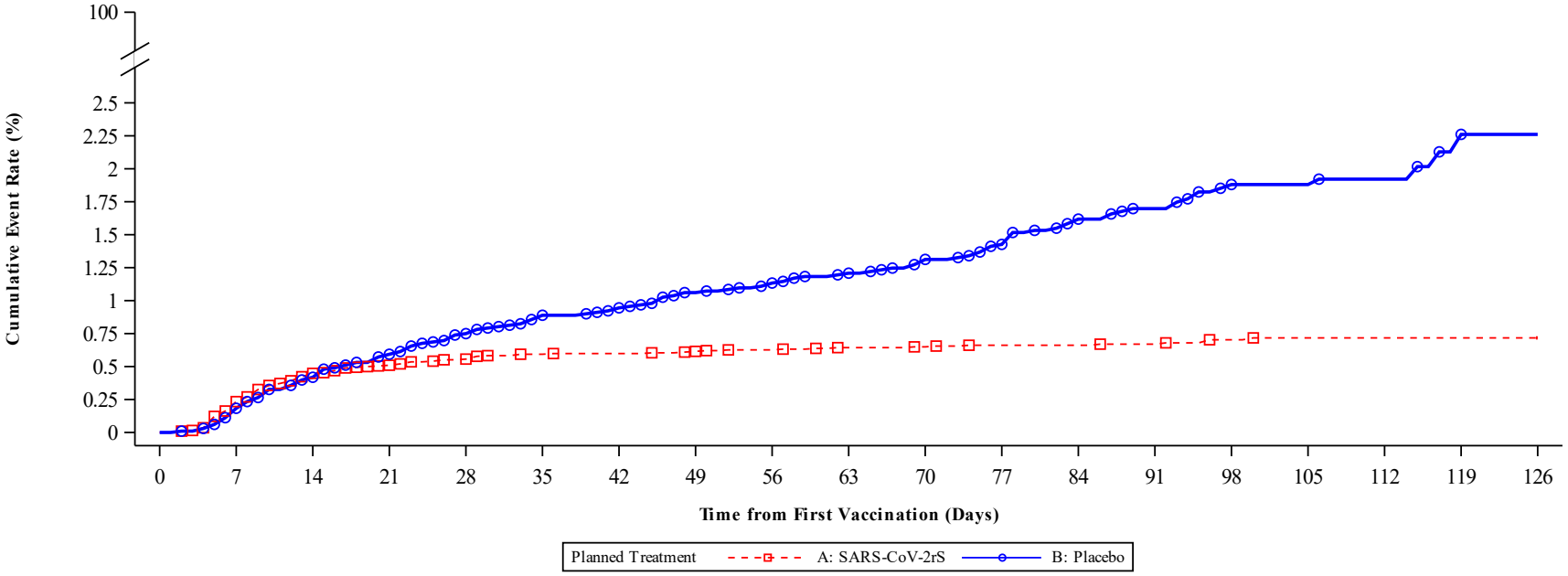
Table 10. COVID-19 Cases From Randomization, Full Analysis Set, Study 301

First COVID-19 Occurrence	NVX-CoV2373 Cases/N (%) (Mean Incidence Rate/ 1,000 Person-Years)	Placebo Cases/N (%) (Mean Incidence Rate/ 1,000 Person-Years)	Vaccine Efficacy (VE)%[1] (95% CI)
After Dose 1	133/19714 (0.67) (26.94)[2]	156/9868 (1.58) (65.63)[2]	58.95% (48.24, 67.44)
Any time after Dose 1 to before Dose 2	106/19714 (0.54) (80.25)[2]	64/9868 (0.65) (96.52)[2]	16.85% (-13.43, 39.05)
Any time after Dose 2	27/18934 (0.14) (7.32)[2]	92/9374 (0.98) (52.58)[2]	86.07% (78.61, 90.93)

Source: Adapted from EUA 28237 Amendment 17, Table 7. Estimates of the incidence rates were calculated by the Biostatistics reviewer.
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease-2019; VE=vaccine efficacy.
N=number of subjects in cohort.
1. VE and 95% CI calculated using Modified Poisson regression with logarithmic link function and treatment group and age strata as fixed effects and robust error variance (Zou, 2004).
2. Mean incidence rate was estimated with weighting for age strata (18 to <65 years of age or ≥65 years of age) reflective of the distribution seen in the study population.

Cumulative incidence of mild to severe COVID-19 in the FAS was similar in both the NVX-CoV2373 and placebo arms until approximately Day 21 after the first vaccination, at which time more cases began accumulating in the placebo arm (Figure 1).

Figure 1. Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 with Onset from First Vaccination in Adult Participants Who Received at Least 1 Dose of Study Vaccine Regardless of Baseline Serostatus, Full Analysis Set, Study 301



	No of cumulative events																		
Placebo	0	18	41	58	73	86	91	101	107	113	121	129	141	145	152	152	153	156	156
SARS-CoV-2 rS	0	46	88	100	109	116	117	120	122	125	126	128	128	129	132	133	133	133	133
	No at risk																		
Placebo	9868	9800	9720	9653	9410	9180	8773	8421	8082	7790	7482	6730	5654	4513	3445	2544	1500	739	524
SARS-CoV-2 rS	19714	19609	19483	19372	19000	18755	18311	17931	17568	17239	16863	15389	13015	10532	7925	5808	3181	1335	753

Source: EUA 28237 Amendment 24, Figure 1.
Abbreviations: COVID-19=coronavirus disease-2019; PCR=polymerase chain reaction

Efficacy Against COVID-19 Among Variants

Although secondary and exploratory efficacy endpoints included efficacy against variants that were and were not considered variants of concern (VOC) or variants of interest (VOI) at the time of the primary efficacy analysis, in the interim the circulating variants and CDC classification of VOC/VOI have changed. Therefore, this analysis is less relevant to the current epidemiology of SARS-CoV-2. Of the 96 cases in the primary efficacy analysis through September 27, 2021, 75 had sequence data available. Of the 75 cases with sequence data, the majority were due to the Alpha (53%), Iota (11%), or Epsilon (7%) variants. As of the time of this writing, none of the variants identified in the primary efficacy analysis are considered VOC/VOI.

Vaccine Efficacy in Protecting Against PCR-Confirmed Moderate to Severe COVID-19

A total of 13 moderate to severe COVID-19 cases were reported in the placebo arm, and none were reported in the NVX-CoV2373 arm, resulting in VE of 100% (95% CI 85.4, 100.0).

Subgroup Analyses of Vaccine Efficacy

VE across the subgroups was comparable to the overall study population; however, lower efficacy rates were observed for participants of Hispanic/Latino ethnicity (77.0% [95% CI 48.7, 90.0]). Due to the small numbers of participants in some subgroups, the CI around the point estimate of VE are wide, which limits the interpretability of the analyses.

Table 11. Analysis of Efficacy by Demographics and COVID-19 Risk Conditions, COVID-19 Starting 7 Days After Dose 2, Per-Protocol Efficacy Set, Study 301

Characteristic	NVX-CoV2373 Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Placebo Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Vaccine Efficacy[2] (VE)% (95% CI)
Age (years)	--	--	--
18 to <65	15/15228 (0.099) (5.70)	75/7417 (1.011) (63.79)	91.06 (84.44, 94.87)
65 to <75	2/1764 (0.113) (6.56)	3/835 (0.359) (23.33)	71.86 (-68.37, 95.30)
75 and older	0/280 (0) (0.00)	1/133 (0.752) (44.93)	100.00 (-1699.39, 100.00)[4]
Sex	--	--	--
Male	7/8989 (0.078) (3.88)	29/4227 (0.686) (37.29)	89.60 (76.26, 95.44)
Female	10/8283 (0.121) (4.84)	50/4158 (1.203) (52.47)	90.77 (81.80, 95.32)
Race	--	--	--
White	13/13124 (0.099) (4.98)	59/6350 (0.929) (51.65)	90.36 (82.43, 94.71)
Black or African American	1/1881 (0.053) (3.01)	8/947 (0.845) (49.56)	93.93 (51.48, 99.24)
American Indian or Alaska Native[4]	1/1068 (0.094) (4.45)	6/522 (1.149) (54.75)	91.88 (32.63, 99.02)
Native Hawaiian or Other Pacific Islander	0/47 (0) (0.00)	0/10 (0) (0.00)	NE[3]
Asian	0/757 (0) (0.00)	5/375 (1.333) (85.72)	100.00 (51.90, 100.00)[3]
Multiple	2/296 (0.676) (38.44)	0/137 (0) (0.00)	NE[3]

Characteristic	NVX-CoV2373 Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Placebo Cases[1] /N (%) (Mean Incidence Rate/ 1,000 person-years)	Vaccine Efficacy[2] (VE)% (95% CI)
Ethnicity	--	--	--
Hispanic/Latino	9/3707 (0.243) (13.09)	18/1801 (0.999) (56.80)	76.96 (48.72, 89.65)
Not Hispanic/Latino	8/13526 (0.059) (2.93)	61/6572 (0.928) (50.63)	94.22 (87.93, 97.23)
Age (years) and risk for severe COVID-19[5]	--	--	--
18 to <65 and not at risk	9/8271 (0.109) (6.32)	37/3966 (0.933) (60.02)	89.47 (78.19, 94.92)
18 to <65 and at risk	6/6957 (0.086) (4.97)	38/3451 (1.101) (67.94)	92.68 (82.69, 96.91)
≥65 and not at risk	1/919 (0.109) (6.50)	1/388 (0.258) (16.56)	60.75 (-2981.22, 99.50)[3]
≥65 and at risk	1/1125 (0.089) (5.02)	3/580 (0.517) (33.17)	84.85 (-88.66, 99.71)[3]
High-risk condition[6]	--	--	--
Yes	16/16455 (0.097) (4.24)	78/7972 (0.978) (46.42)	90.87 (84.38, 94.67)
No	1/817 (0.122) (7.15)	1/413 (0.242) (15.55)	54.02 (-3509.45, 99.41)[3]
BMI >30 kg/m^2	6/6344 (0.095) (3.63)	36/3157 (1.140) (46.11)	92.13 (81.31, 96.69)

Source: EUA 28237 Amendment 24, Table 7.
Abbreviations: BMI=body mass index; CI=confidence interval; COVID-19=coronavirus disease-2019; eCRF=electronic case report form; NE=not estimable in the event the test for exact binomial proportion cannot be conducted; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=relative risk; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; VE=vaccine efficacy
1. Case defined as first occurrence of PCR-confirmed mild, moderate or severe COVID-19 disease with onset from 7 days after second injection within the surveillance period.
2. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of study vaccine (NVX-CoV2373 or placebo) in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (September 27, 2021), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) early withdrawal, or (vi) first dose of crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 disease criteria were censored at date of the PCR-positive.
3. In case when there are zero cases in either treatment group or the total number of cases in both treatment groups combined <5, VE and 95% CI is calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases and is adjusted for total surveillance time.
4. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were enrolled at sites in the United States.
5. High-risk adults were 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; 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.
6. Health risks include obesity (BMI >30 kg/m^2), chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and/or chronic kidney disease.
Note: RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group and strata (age-group and pooled region) as fixed effects and robust error variance (Zou, 2004) fitted separately to each subgroup.

6.2.5 Safety

6.2.5.1 Safety Overview

Safety analyses presented in this review are derived from safety data available from both the

pre- and post-crossover periods of the study, with a database cutoff date of September 27, 2021. To provide additional safety data from longer-term follow up, data on MAAEs, SAEs, AESIs were provided through a database extraction date of February 17, 2022 (data cleaning not completed by the Sponsor). As described in Section 6.2.1, participants could cross over to receive either placebo or NVX-CoV2373 in a blinded fashion. Therefore, data collected in the pre-crossover period provides placebo-controlled data, whereas data collected in the post-crossover period are only from participants who received NVX-CoV2373 at some point during the study, limiting comparisons between the treatment arms. Additionally, based on whether participants crossed over and when, the duration of follow up in the pre-crossover period varied by individual participant, which complicated the interpretation of analyses. As described in Section 6.2.2, safety data for 289 participants was excluded from safety analysis populations due to data quality issues (Site 151) and vaccine administration errors (Site 76).

Additionally, a total of 45 participants received NVX-CoV2373 in both the pre- and post-crossover periods. These 45 participants were included in the denominator for both the pre-crossover and post-crossover counts.

The duration of safety follow-up for the pre- and post-crossover periods, as of the September 27, 2021, data cutoff date, is described in the table below.

Table 12. Study Safety Analyses Populations and Follow Up Time, Safety Analysis Set, Study 301

Population	Pre-crossover Received NVX-CoV2373 N=19735	Pre-crossover Received Placebo N=9847	Pre-crossover Total N=29582	Post-crossover Received Placebo N=15298	Post-crossover Received NVX-CoV2373 N=6416	Post-crossover Total N=21669
First vaccination series	--	--	--	--	--	--
Completed 2 doses, n	19111	9416	28527	NA	NA	NA
Median follow up post-Dose 2, months	2.5	2.5	2.5	NA	NA	NA
Completed at least 1 month follow up post Dose 2[1], n (%)	18630 (97.5)	8869 (94.2)	27499 (96.4)	NA	NA	NA
Completed at least 2 months follow up post-Dose 2[1], n (%)	14825 (77.8)	6852 (72.8)	21677 (76.0)	NA	NA	NA
Crossover vaccination series	--	--	--	--	--	--
Completed 4 doses, n	NA	NA	NA	15084	6346	21387
Median follow up post-Dose 4, months	NA	NA	NA	4.4	4.4	4.4
Completed at least 1 month follow up post-Dose 4[2], n (%)	NA	NA	NA	15027 (99.6)	6321 (99.6)	21305 (99.6)
Completed at least 2 months follow up post-Dose 4[2], n (%)	NA	NA	NA	14934 (99.0)	6287 (99.1)	21178 (99.0)

Source: EUA 28237 Amendment 17.
1. Denominator based on number of participants who completed 2 doses.
2. Denominator based on number of participants who completed 4 doses.
Abbreviations: n=number of participants with indicated completion; N=number of participants in cohort; NA=not applicable
Note: Follow up post Dose 2 is defined as the time from initial Dose 2 date to the earliest date of early termination, date of death and date of first crossover dose and date of data extract (September 27, 2021). Follow up post Dose 4 is defined as the time from second crossover dose date to the earliest date of early termination, date of death and date of data extract (September 27, 2021).
Note: Safety Analysis Set included all participants who received at least 1 dose of study vaccine/placebo. Participants in the Safety Analysis Set were analyzed according to the treatment actually received. In cases where information was available that indicated that a participant received both active and placebo vaccine during the initial period, the participant was analyzed as part of the active group.
NA: not applicable.

Table 13 provides an overview of the safety data reported as of the September 27, 2021, data cutoff date.

Table 13. Safety Overview, Safety Analysis Set, Study 301

Subjects Reporting at Least One	NVX-CoV2373	Placebo
Solicited injection site reaction within 7 days[1], n/N (%)	--	--
Dose #1	10494/18135 (57.9)	1900/8982 (21.2)
Grade 3	196/18135 (1.1)	22/8982 (0.2)
Grade 4	0/18135 (0)	0/8982 (0)
Dose #2	13524/17196 (78.6)	1802/8339 (21.6)
Grade 3	1141/17196 (6.6)	24/8339 (0.3)
Grade 4	5/17196 (<0.1)	1/8339 (<0.1)
Solicited systemic adverse reaction within 7 days[1], n/N (%)	--	--
Dose #1	8614/18135 (47.5)	3593/8982 (40.0)
Grade 3	419/18135 (2.3)	187/8982 (2.1)
Grade 4	15/18135 (<0.1)	4/8982 (<0.1)
Dose #2	11920/17196 (69.3)	2990/8339 (35.9)
Grade 3	2058/17196 (12.0)	170/8339 (2.0)
Grade 4	18/17196 (0.1)	5/8339 (<0.1)
Unsolicited adverse event[2], n/N (%)	--	--
Non-serious unsolicited AE	--	--
Pre-crossover period	2285/19735 (11.6)	1101/9847 (11.2)
Post-crossover period	522/6416 (8.1)	850/15298 (5.6)
Related non-serious unsolicited AE		
Pre-crossover period	481/19735 (2.4)	148/9847 (1.5)
Post-crossover period	131/6416 (2.0)	54/15298 (0.4)
Grade 3 non-serious unsolicited AE	--	--
Pre-crossover period	88/19735 (0.4)	37/9847 (0.4)
Post-crossover period	18/6416 (0.3)	20/15298 (0.1)
Related Grade 3 non-serious unsolicited AE		
Pre-crossover period	18/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	3/6416 (<0.1)	1/15298 (<0.1)
Medically attended adverse event, n/N (%)	--	--
Pre-crossover period	1144/19735 (5.8)	558/9847 (5.7)
Post-crossover period	299/6416 (4.7)	610/15298 (4.0)
Related MAAE		
Pre-crossover period	95/19735 (0.5)	29/9847 (0.3)
Post-crossover period	22/6416 (0.3)	23/15298 (0.2)
SAE, n/N (%)	--	--
Pre-crossover period	199/19735 (1.0)	108/9847 (1.1)
Post-crossover period	88/6416 (1.4)	178/15298 (1.2)
Related SAE	--	--
Pre-crossover period	5/19735 (<0.1)	3/9847 (<0.1)
Post-crossover period	2/6416 (<0.1)	3/15298 (<0.1)
AESI (PIMMCs)[3], n/N (%)	--	--
Pre-crossover period	25/19735 (0.1)	11/9847 (0.1)
Post-crossover period	10/6416 (0.2)	5/15298 (<0.1)
AESI (PIMMCs)[4], n/N (%)	--	--
Pre-crossover period	24/19735 (0.1)	14/9847 (0.1)
Post-crossover period	6/6416 (<0.1)	14/15298 (<0.1)
AESI (PIMMCs)[5]	--	--
Pre-crossover period	35/19735 (0.2)	19/9847 (0.2)
Post-crossover period	11/6416 (0.2)	15/15298 (<0.1)

Subjects Reporting at Least One	NVX-CoV2373	Placebo
AESI (related to COVID-19), n/N (%)	--	--
Pre-crossover period	7/19735 (<0.1)	6/9847 (<0.1)
Post-crossover period	3/6416 (<0.1)	3/15298 (<0.1)
Deaths, n/N (%)	--	--
Pre-crossover period	11/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	6/6416 (<0.1)	10/15298 (<0.1)
AE leading to discontinuation of the vaccine, n/N (%)	--	--
Pre-crossover period	67/19735 (0.3)	22/9847 (0.2)
Post-crossover period	4/6416 (<0.1)	13/15298 (<0.1)

Source: EUA 28237 Amendment 35. Response to information request 34, page 2, Table 21.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease-2019; MAAE=medically attended adverse event; PIMMC=potential immune-mediated medical condition; SAE=serious adverse event.
N=number of participants in cohort; n=number of participants with indicated event.
1. Reported as of the data cutoff date of September 27, 2021.
2. Reported from Dose 1 through 28 days post dose 2.
3. Based on investigator reporting.
4. Based on protocol-defined criteria.
5. Based on investigator reporting and protocol-defined criteria.

AEs Leading to Discontinuation

In the pre-crossover period, the proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the NVX-CoV2373 (0.3%) and placebo (0.2%) arms. The most common event leading to discontinuation in the NVX-CoV2373 arm was COVID-19 (n=5; 0.03%). Of the most frequently reported events leading to discontinuation of vaccine (occurring in ≥3 participants) in the NVX-CoV2373 arm, most were consistent with systemic reactogenicity (diarrhea, pyrexia, headache, and nausea). The remaining events (cardiovascular accident, acute kidney injury, cardiac arrest, and cough) are discussed in the safety review below.

In the post-crossover period, the proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the participants who crossed over to receive NVX-CoV2373 (0.06%) and participants who crossed over to receive placebo (0.08%). A total of 4 participants who crossed over to receive NVX-CoV2373 reported 5 events leading to discontinuation of the vaccine, including acute myocardial infarction, COVID-19, costochondritis, mental status changes, and overdose.

AEs Leading to Study Withdrawal

In the pre-crossover period, the proportion of participants AEs leading to study withdrawal were comparable between the NVX-CoV2373 (0.2%) and placebo (0.1%) arms. The most common event leading to discontinuation in the NVX-CoV2373 arm was COVID-19 (n=5; 0.03%). Of the most frequently reported events leading to discontinuation of vaccine (≥3 participants) in the NVX-CoV2373 arm, most were consistent with systemic reactogenicity (diarrhea, pyrexia, headache, and nausea). The remaining events (cardiovascular accident, acute kidney injury, cardiac arrest, and cough) are discussed in the safety review below.

In the post-crossover period, proportion of participants reporting AEs leading to discontinuation of the vaccine were comparable between the participants who crossed over to receive NVX-CoV2373 (0.2%) and participants who crossed over to receive placebo (0.1%). For participants who crossed over to receive NVX-CoV2373, there were no events leading to study withdrawal reported by more than 1 participant. The only event leading to withdrawal reported by more than 1 participant who crossed over to receive placebo was death (n=2).

6.2.5.2 Solicited Adverse Reactions

Solicited local and systemic ARs with onset within 7 days after vaccination are presented in the tables below for participants in the Safety Analysis Set, stratified by age (18 to 64 years; ≥65 years). These data were only collected in the pre-crossover period. Solicited ARs were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain/tenderness, erythema, and swelling) and systemic reactions (fatigue/malaise, headache, muscle pain, nausea, and fever). Data on solicited local ARs and systemic ARs were provided by 92.0% of participants after Dose 1 and by 87.1% after Dose 2 in the NVX-CoV2373 arm and by 91.2% of participants after Dose 1 and 84.7% after Dose 2 in the placebo arm.

Local Adverse Reactions

All solicited local ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm than in the placebo arm, and the proportion of participants reporting solicited local ARs increased after the second dose of NVX-CoV2373. The most frequently reported local AR was injection site pain/tenderness. Grade 3 ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm than in the placebo arm and increased in frequency following the second dose of NVX-CoV2373. Grade 4 ARs were infrequently reported after Dose 2 of NVX-CoV2373 (<0.1%) and placebo (<0.1%) .

For any solicited local AR, the median time to onset was 2 days (range 1-7) for Doses 1 and 2 in the NVX-CoV2373 arm and 2 and 1 days (range 1-7 days) for Dose 1 and 2, respectively, in the placebo arm. The median time to onset for each event was between 1 and 3 days. The median duration of any solicited local AR was 2 and 3 days (range 1-7) for Doses 1 and 2, respectively, in the NVX-CoV2373 arm and 1 day (range 1-7) for Doses 1 and 2 in the placebo arm. For each local AR, the median duration within the reactogenicity period of 7 days was between 1 and 2 days in the NVX-CoV2373 arm and 1 day in the placebo arm. The median duration of any solicited local AR (including events persisting beyond the 7-day period) was 2 and 3 days in the NVX-CoV2373 arm after Dose 1 (range 1-112 days) and 3 days after Dose 2 (range 1-252 days), respectively and 1 day in the placebo arm for both Dose 1 (range 1-19 days) and Dose 2 (range 1-55 days).

Solicited local ARs persisting beyond the 7-day reactogenicity period were reported by a higher proportion of participants in the NVX-CoV2373 arm (0.1% after Dose 1 and 0.2% after Dose 2) compared with the placebo arm (0.02% after Dose 1 and Dose 2). Of the local solicited ARs persisting beyond 7 days, pain/tenderness were the most common.

In an analysis of local ARs by age group, all local ARs were reported more frequently among participants 18-64 years of age compared to participants ≥65 years of age. Overall rates of each local AR and Grade 3 ARs were lower in participants ≥65 years of age, and Grade 4 ARs were only reported in the younger participants. Table 14 provides rates of local ARs by treatment arm, dose, and age group.

Table 14. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Age Group, Safety Analysis Set, Study 301

Event	NVX-CoV2373 Dose 1	Placebo Dose 1	NVX-CoV2373 Dose 2	Placebo Dose 2
Participants 18 to <65 years	N=15884	N=7868	N=15148	N=7361
Any solicited local reaction, n (%)	--	--	--	--
Any (Grade ≥1)	9633 (60.7)	1722 (21.9)	12261 (80.9)	1637 (22.2)
Grade 3	182 (1.2)	19 (0.2)	1084 (7.2)	22 (0.3)
Grade 4	0	0	5 (<0.1)	1 (<0.1)
Pain/tenderness, n (%)	--	--	--	--
Any (Grade ≥1)	9604 (60.5)	1706 (21.7)	12234 (80.8)	1623 (22.1)
Grade 3	174 (1.1)	17 (0.2)	951 (6.3)	20 (0.3)
Grade 4	0	0	5 (<0.1)	1 (<0.1)
Erythema, n (%)	--	--	--	--
Any (Grade ≥1)	151 (1.0)	21 (0.3)	1040 (6.9)	26 (0.4)
Grade 3	3 (<0.1)	0	134 (0.9)	2 (<0.1)
Grade 4	0	0	0	0
Swelling, n (%)	--	--	--	--
Any (Grade ≥1)	137 (0.9)	24 (0.3)	943 (6.2)	22 (0.3)
Grade 3	7 (<0.1)	3 (<0.1)	82 (0.5)	1 (<0.1)
Grade 4	0	0	0	0
Participants ≥65 years	N=2251	N=1114	N=2048	N=978
Any solicited local reaction, n (%)	--	--	--	--
Any (Grade ≥1)	861 (38.3)	178 (16.0)	1263 (61.7)	165 (16.9)
Grade 3	14 (0.6)	3 (0.3)	57 (2.8)	2 (0.2)
Grade 4	0	0	0	0
Pain/tenderness, n (%)	--	--	--	--
Any (Grade ≥1)	854 (37.9)	175 (15.7)	1258 (61.4)	161 (16.5)
Grade 3	13 (0.6)	3 (0.3)	43 (2.1)	1 (0.1)
Grade 4	0	0	0	0
Erythema, n (%)	--	--	--	--
Any (Grade ≥1)	16 (0.7)	5 (0.5)	99 (4.8)	4 (0.4)
Grade 3	0	0	7 (0.3)	0
Grade 4	0	0	0	0
Swelling, n (%)	--	--	--	--
Any (Grade ≥1)	18 (0.8)	1 (0.1)	111 (5.4)	4 (0.4)
Grade 3	1 (<0.1)	0	8 (0.4)	1 (0.1)
Grade 4	0	0	0	0

Source: EUA 28237 Amendment 28 Tables 14.3.2.1.1a_1 and 14.3.2.1.1a_2.
Abbreviation: ER=emergency room; n=number of participants experiencing the adverse event
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table. Two adverse reactions were re-characterized: tenderness to pain and muscle swelling to swelling.
Pain: Grade 1: Does not interfere with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity; Grade 3: Any use of narcotic pain reliever or prevents daily activity; and Grade 4: Emergency room visit or hospitalization.
Tenderness: Grade 1: Mild discomfort to touch; Grade 2: Discomfort with movement; Grade 3: Significant discomfort at rest; and Grade 4: ER visit or hospitalization.
Erythema: Grade 1: 2.5 to 5 cm; Grade 2: 5.1 to 10 cm; Grade 3: >10 cm; and Grade 4: Necrosis or exfoliative dermatitis.
Swelling/induration (should be evaluated and graded using the functional scale as well as the actual measurement): Grade 1: 2.5 to 5 cm and does not interfere with activity; Grade 2: 5.1 to 10 cm or interferes with activity; Grade 3: >10 cm or prevents daily activity; and Grade 4: Necrosis.

Solicited Systemic Adverse Reactions

Solicited systemic ARs were reported by a higher proportion of participants in the NVX-CoV2373 arm compared to the placebo arm, overall and for each solicited AR. The proportion of

participants with systemic solicited ARs after Dose 2 increased in the NVX-CoV2373 arm but remained comparable to after Dose 1 in the placebo arm. After Dose 1, the proportion of participants with Grade 3 and 4 solicited systemic ARs was comparable between the treatment arms and generally low (<1.5% and <0.1%, respectively). After Dose 2, the proportion of participants with Grade 3 and 4 solicited systemic ARs (overall and for each event) increased in the NVX-CoV2373 arm but remained comparable to after Dose 1 in the placebo arm. In the NVX-CoV2373arm, 13% of participants reported any Grade 3 solicited systemic AR after Dose 2, compared to 2.1% of participants in the placebo arm.

In both treatment groups and for both Dose 1 and 2, fatigue/malaise, headache, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs.

For any solicited systemic AR, the median time to onset was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms. The median time to onset for each event was between 2 and 4 days for each event, with the longest latency observed for fever following Dose 1 in both treatment arms. For each systemic AR, the median duration within the reactogenicity period of 7 days was 1 day in both treatment arms. For any systemic AR, the median duration (including events persisting beyond the 7-day period) was 2 days both treatment arms for both doses (range 1-370 days and 1- 93 days for Dose 1 and 2, respectively in the NVX-CoV2373 arm and 1-186 and 1-239 days for Dose 1 and 2, respectively, in the placebo arm).

Any solicited systemic AR persisting beyond the 7-day reactogenicity period was reported by a comparable proportion of participants in the NVX-CoV2373 arm (0.3% after Dose 1 and 0.2% after Dose 2) and the placebo arm (0.2% after Dose 1 and Dose 2). Of the solicited systemic ARs persisting beyond 7 days, headache was the most common in both treatment arms.

In a subgroup analysis by age, all systemic ARs were reported more frequently by participants 18-64 years of age compared to participants ≥65 years of age.

Table 15. Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set, Participants 18 to <65 Years of Age, Study 301

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Any solicited systemic reaction, n (%)	--	--	--	--
Any (Grade ≥1)	7889 (49.7)	3242 (41.2)	10922 (72.1)	2714 (36.9)
Grade 3	383 (2.4)	175 (2.2)	1968 (13.0)	155 (2.1)
Grade 4	14 (0.1)	4 (0.1)	16 (0.1)	5 (0.1)
Fever, n (%)	--	--	--	--
Any (Grade ≥1)	56 (0.4)	31 (0.4)	941 (6.2)	16 (0.2)
Grade 1	32 (0.2)	16 (0.2)	620 (4.1)	11 (0.2)
Grade 2	13 (0.1)	7 (0.1)	259 (1.7)	3 (<0.1)
Grade 3	7 (<0.1)	7 (0.1)	60 (0.4)	2 (<0.1)
Grade 4	4 (<0.1)	1 (<0.1)	2 (<0.1)	0
Headache, n (%)	--	--	--	--
Any (Grade ≥1)	4158 (26.2)	1866 (23.7)	7128 (47.1)	1492 (20.3)
Grade 1	3153 (19.9)	1437 (18.3)	3777 (24.9)	1102 (15.0)
Grade 2	869 (5.5)	370 (4.7)	2854 (18.8)	352 (4.8)
Grade 3	132 (0.8)	58 (0.7)	492 (3.3)	36 (0.5)
Grade 4	4 (<0.1)	1 (<0.1)	5 (<0.1)	2 (<0.1)

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Fatigue/malaise, n (%)	--	--	--	--
Any (Grade ≥1)	4892 (30.8)	2095 (26.6)	8825 (58.3)	1889 (25.7)
Grade 1	2396 (15.1)	1031 (13.1)	2565 (16.9)	890 (12.1)
Grade 2	2239 (14.1)	950 (12.1)	4662 (30.8)	882 (12.0)
Grade 3	249 (1.6)	113 (1.4)	1591 (10.5)	114 (1.6)
Grade 4	8 (0.1)	1 (<0.1)	7 (0.1)	3 (<0.1)
Muscle pain (myalgia), n (%)	--	--	--	--
Any (Grade ≥1)	3827 (24.1)	1073 (13.6)	7682 (50.7)	900 (12.2)
Grade 1	2831 (17.8)	756 (9.6)	3471 (22.9)	613 (8.3)
Grade 2	915 (5.8)	285 (3.6)	3401 (22.5)	255 (3.5)
Grade 3	79 (0.5)	31 (0.4)	805 (5.3)	28 (0.4)
Grade 4	2 (<0.1)	1 (<0.1)	5 (<0.1)	4 (0.1)
Joint pain (arthralgia), n (%)	--	--	--	--
Any (Grade ≥1)	1260 (7.9)	522 (6.6)	3542 (23.4)	504 (6.9)
Grade 1	776 (4.9)	323 (4.1)	1487 (9.8)	317 (4.3)
Grade 2	434 (2.7)	174 (2.2)	1657 (10.9)	163 (2.2)
Grade 3	49 (0.3)	25 (0.3)	393 (2.6)	22 (0.3)
Grade 4	1 (<0.1)	0	5 (<0.1)	2 (<0.1)
Nausea/vomiting, n (%)	--	--	--	--
Any (Grade ≥1)	1069 (6.7)	466 (5.9)	1822 (12.0)	417 (5.7)
Grade 1	850 (5.4)	364 (4.6)	1305 (8.6)	317 (4.3)
Grade 2	197 (1.2)	93 (1.2)	484 (3.2)	91 (1.2)
Grade 3	18 (0.1)	7 (0.1)	26 (0.2)	7 (0.1)
Grade 4	4 (<0.1)	2 (<0.1)	7 (0.1)	2 (<0.1)

Source: EUA 28237 Amendment 28, Tables 14.3.2.2.1a_1 and 14.3.2 2.1a_2.
Abbreviations: ER=emergency room; IV=intravenous.
n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary.
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Grade 1: 38.0 to 38.4°C/100.4 to 101.1°F; Grade 2: 38.5 to 38.9°C/101.2 to 102.0°F; Grade 3: 39.0 to 40°C/102.1 to 104°F; and Grade 4: >40°C/>104°F.
Headache: Grade 1: No interference with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; and Grade 4: ER visit or hospitalization.
Fatigue/malaise: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Myalgia/arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Nausea/vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient IV hydration; and Grade 4: ER visit or hospitalization for hypotensive shock.

Table 16. Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants ≥65 Years of Age, Study 301

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Any solicited systemic reaction, n (%)	--	--	--	--
Any (Grade ≥1)	725 (32.2)	351 (31.5)	998 (48.7)	276 (28.2)
Grade 3	36 (1.6)	12 (1.1)	90 (4.4)	15 (1.5)
Grade 4	1 (<0.1)	0	2 (0.1)	0
Fever, n (%)	--	--	--	--
Any (Grade ≥1)	8 (0.4)	3 (0.3)	40 (2.0)	7 (0.7)
Grade 1	4 (0.2)	2 (0.2)	30 (1.5)	5 (0.5)
Grade 2	3 (0.1)	1 (0.1)	8 (0.4)	1 (0.1)
Grade 3	1 (<0.1)	0	2 (0.1)	1 (0.1)
Grade 4	0	0	0	0
Headache, n (%)	--	--	--	--
Any (Grade ≥1)	344 (15.3)	184 (16.5)	502 (24.5)	144 (14.7)
Grade 1	292 (13.0)	153 (13.7)	378 (18.5)	117 (12.0)
Grade 2	39 (1.7)	27 (2.4)	105 (5.1)	25 (2.6)
Grade 3	12 (0.5)	4 (0.4)	18 (0.9)	2 (0.2)
Grade 4	1 (<0.1)	0	1 (0.1)	0
Fatigue/malaise, n (%)	--	--	--	--
Any (Grade ≥1)	444 (19.7)	202 (18.1)	714 (34.9)	182 (18.6)
Grade 1	246 (10.9)	105 (9.4)	295 (14.4)	96 (9.8)
Grade 2	175 (7.8)	92 (8.3)	351 (17.1)	73 (7.5)
Grade 3	23 (1.0)	5 (0.5)	68 (3.3)	13 (1.3)
Grade 4	0	0	0	0
Muscle pain (myalgia), n (%)	--	--	--	--
Any (Grade ≥1)	284 (12.6)	125 (11.2)	561 (27.4)	102 (10.4)
Grade 1	222 (9.9)	88 (7.9)	344 (16.8)	68 (7.0)
Grade 2	59 (2.6)	33 (3.0)	185 (9.0)	32 (3.3)
Grade 3	3 (0.1)	4 (0.4)	32 (1.6)	2 (0.2)
Grade 4	0	0	0	0
Joint pain (arthralgia), n (%)	--	--	--	--
Any (Grade ≥1)	139 (6.2)	71 (6.4)	271 (13.2)	63 (6.4)
Grade 1	86 (3.8)	39 (3.5)	141 (6.9)	34 (3.5)
Grade 2	49 (2.2)	28 (2.5)	113 (5.5)	27 (2.8)
Grade 3	4 (0.2)	4 (0.4)	16 (0.8)	2 (0.2)
Grade 4	0	0	1 (0.1)	0

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Nausea/vomiting, n (%)	--	--	--	--
Any (Grade ≥1)	81 (3.6)	32 (2.9)	108 (5.3)	35 (3.6)
Grade 1	69 (3.1)	26 (2.3)	84 (4.1)	28 (2.9)
Grade 2	12 (0.5)	6 (0.5)	21 (1.0)	7 (0.7)
Grade 3	0	0	3 (0.2)	0
Grade 4	0	0	0	0

Source: EUA 28237 Amendment 28, Tables 14.3.2.2.1a_1 and 14.3.2 2.1a_2.
Abbreviations: ER=emergency room; IV=intravenous.
n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least 1 day of the reactogenicity diary.
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Fever: Grade 1: 38.0 to 38.4°C/100.4 to 101.1°F; Grade 2: 38.5 to 38.9°C/101.2 to 102.0°F; Grade 3: 39.0 to 40°C/102.1 to 104°F; and Grade 4: >40°C/>104°F.
Headache: Grade 1: No interference with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; and Grade 4: ER visit or hospitalization.
Fatigue/malaise: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Myalgia/arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Nausea/vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient IV hydration; and Grade 4: ER visit or hospitalization for hypotensive shock.

Immediate Adverse Events

The Sponsor did not specify AEs or ARs that were to be collected in the immediate post-vaccination period.

6.2.5.3 Unsolicited Adverse Events

The determination of severity for all unsolicited AE was made by study investigators based on protocol-specified definitions of severity mild to potentially life threatening. Causal relationship to study vaccine was determined by study investigators and classified as “related” or “not related.”

Unsolicited Adverse Events (Pre-Crossover)

In the pre-crossover period through the September 27, 2021, data cutoff, the proportions of participants reporting any non-serious unsolicited AE were comparable between the NVX-CoV2373 (11.6%) and placebo (11.2%) arms. There was no MedDRA preferred term (PT) reported by more than 1% of participants in either group; therefore, Table 17 summarizes unsolicited AEs occurring in ≥1% of participants by MedDRA system organ class (SOCs). The overall frequency of unsolicited adverse events by SOC were similar between groups, although imbalances in the SOC of General disorders and administration site conditions and Blood and lymphatic system disorders were noted, largely due to AEs associated with reactogenicity (including chills, injection site pruritis, and influenza-like illness) and lymphadenopathy, respectively.

Lymphadenopathy-related events were reported by 0.3% of participants in the NVX-CoV2373 arm and 0.1% of participants in the placebo arm. These events included lymphadenopathy, lymphadenitis, lymph node pain, and axillary pain and were plausibly related to vaccination. All

lymphadenopathy-related reactions occurred in participants 18 through 64 years of age. Severe non-serious unsolicited AEs were infrequent and reported by a comparable proportion of participants in each treatment arm (0.4% in each). The most commonly reported (≥0.1% of participants) severe unsolicited event in the NVX-CoV2373 arm was fatigue (n=10, 0.1%). Related severe events were reported by a higher proportion of participants in the NVX-CoV2373 arm (0.1%) compared to the placebo arm (0.05%). Of the severe related events in the NVX-CoV2373 arm, fatigue was the only event reported by more than 1 participant (n=3).

Unsolicited AEs considered related by the investigator were reported by 2.4% of participants in the NVX-CoV2373 arm and 1.5% of participants in the placebo arm. The most frequently reported related AEs in the NVX-CoV2373 arm included chills, injection site pruritis, and lymphadenopathy.

Table 17. Pre-Crossover Period: Frequency of Unsolicited AEs Reported Within 49 Days With Occurrence in ≥1% of Participants, Safety Analysis Set, Study 301

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
Infections and infestations	520/19735 (2.6)	25/19735 (0.1)	301/9847 (3.1)	20/9847 (0.2)
General disorders and administration site conditions	330/19735 (1.7)	19/19735 (0.1)	109/9847 (1.1)	7/9847 (0.1)
Nervous system disorders	328/19375 (1.7)	12/19735 (0.1)	171/9847 (1.7)	10/9847 (0.1)
Respiratory, thoracic and mediastinal disorders	356/19735 (1.8)	12/139735 (0.1)	175/9847 (1.8)	3/9847 (<0.1)
Gastrointestinal disorders	291/19375 (1.5)	12/19735 (0.1)	148/9847 (1.5)	6/9847 (0.1)
Musculoskeletal and connective tissue disorders	239/19375 (1.2)	16/19735 (0.1)	128/9847 (1.3)	2/9847 (<0.1)
Skin and subcutaneous tissue disorders	194/19375 (1.0)	3/19735 (<0.1)	69/9847 (0.7)	1/9847 (<0.1)
Injury, poisoning and procedural complications	189/19735 (1.0)	20/19735 (0.1)	95/9847 (1.0)	11/9847 (0.1)

Source: EUA 28237 Amendment 25 Table Shells, Table 38.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities.
n=number of participants reporting the adverse event at least once; N=number of participants included in the considered cohort in each group
1. Adverse Events coded using MedDRA version 24.0.
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of study vaccine.
Note: Follow-up time for the pre-crossover period is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment. Follow-up time for the post-crossover period is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cutoff (September 27, 2021).

Unsolicited Adverse Events (Post-Crossover)

In the post-crossover period through the September 27, 2021, data cutoff, the proportion of participants reporting any non-serious unsolicited AE was higher for participants who crossed over to receive NVX-CoV2373 (8.1%) compared to participants who crossed over to receive placebo (5.6%). There was no MedDRA PT reported by more than 1% of participants in either arm; therefore, Table 18 summarizes unsolicited AEs occurring in ≥1% of participants by SOC. The overall frequency of unsolicited adverse events by SOC were similar between arms, although imbalances in the SOC of General disorders and administration site conditions and Nervous System disorders were noted, largely due to AEs associated with reactogenicity

(including fatigue, injection site pain/erythema/pruritis/swelling, pain, headache, pyrexia, and chills).

Severe non-serious unsolicited AEs were infrequent and reported by a higher proportion of participants who crossed over to receive NVX-CoV2373 (0.3%) compared to participants who crossed over to receive placebo (0.1%).. Related severe events were reported by a higher proportion of participants who crossed over to receive NVX-CoV2373 (0.05%) compared to participants who crossed over to receive placebo (0.01%). Severe related events in the NVX-CoV2373 arm included diarrhea, headache, and neuralgic amyotrophy (4 days after administration of NVX-CoV2373). Please see Section 6.2.5.4 for additional discussion of the event of neuralgic amyotrophy (Parsonage-Turner syndrome).

Unsolicited AEs considered related by the investigator to study vaccination post-crossover were reported by 2.0% of participants who crossed over to receive NVX-CoV2373 compared to 0.4% of participants who crossed over to receive placebo. This imbalance was largely due to events of injection site pain, fatigue, pyrexia, myalgia, pain, and headache.

Table 18. Post-Crossover Period: Frequency of Unsolicited AEs Reported Within 49 Days With Occurrence in ≥1% of Participants, Safety Analysis Set, Study 301

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373 Any n/N (%)	NVX-CoV2373 Severe n/N (%)	Placebo Any n/N (%)	Placebo Severe n/N (%)
General disorders and administration site conditions	138/6416 (2.2)	5/6416 (0.1)	82/15298 (0.5)	3/15298 (<0.1)
Infections and infestations	109/6416 (1.7)	2/6416 (<0.1)	243/15298 (1.6)	10/15298 (0.1)
Nervous system disorders	77/6416 (1.2)	4/6416 (0.1)	102/15298 (0.7)	7/15298 (<0.1)
Respiratory, thoracic and mediastinal disorders	73/6416 (1.1)	6/6416 (0.1)	130/15298 (0.8)	4/15298 (<0.1)
Gastrointestinal disorders	62/6416 (1.0)	2/6416 (<0.1)	108/15298 (0.7)	7/15298 (<0.1)
Musculoskeletal and connective tissue disorders	65/6416 (1.0)	2/6416 (<0.1)	107/15298 (0.7)	5/15298 (<0.1)

Source: EUA 28237 Amendment 25 Table Shells, Table 38
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities,
n=number of participants reporting the adverse event at least once; N=number of participants included in the considered cohort in each group.
1. Adverse Events coded using MedDRA version 24.0.
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of study vaccine.
Note: Follow-up time for the pre-crossover period is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment. Follow-up time for the post-crossover period is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cutoff (September 27, 2021).

6.2.5.4 Unsolicited Adverse Events of Clinical Interest

Adverse Events of Special Interest

AESIs for Trial 301 included PIMMCs (Potential Immune-Mediated Medical Conditions) and AEs representing complications specific to COVID-19. The AEs representing complications specific to COVID-19 were reviewed, and no concerns for vaccine enhanced disease were identified. PIMMCs are defined in Appendix B and are intended to capture potential autoimmune-mediated conditions that could be associated with adjuvanted vaccines. Three approaches were used to assess AESIs of PIMMCs in the study: 1) investigator reporting; 2) protocol-defined criteria; and

3) investigator reporting and protocol-defined criteria combined. The analyses that follow discuss only PIMMCs identified using protocol-defined criteria.

The proportion of participants with PIMMCs was comparable in the NVX-CoV2373 and placebo arms (0.1% each) during the pre-crossover period through September 27, 2021. A total of 25 PIMMCs were reported by 24 participants in the NVX-CoV2373 arm, and 14 PIMMCs were reported by 14 participants in the placebo arm. The proportions of participants reporting each specific event was comparable between the treatment arms, although the numbers of each event were small. No pattern of events to suggest a specific autoimmune phenomenon associated with vaccination was observed.

Table 19. Potential Immune-Mediated Medical Conditions Reported in the Pre-Crossover Period, Study 301

Preferred Term	NVX-CoV2373 N=19735 N (%)	Placebo N=9847 N (%)
Alopecia areata	1 (0.005)	0 (0)
Ankylosing spondylitis	1 (0.005)	0 (0)
Autoimmune thyroiditis	1 (0.005)	1 (0.01)
Basedow's disease	2 (0.01)	0 (0)
Bell's palsy	3 (0.015)	1 (0.01)
Crohn's disease	1 (0.005)	0 (0)
Erythema nodosum	1 (0.005)	0 (0)
Lichen planus	0 (0)	1 (0.01)
Neuropathy peripheral	3 (0.015)	3 (0.03)
Polymyalgia rheumatica	1 (0.005)	1 (0.01)
Psoriasis	1 (0.005)	1 (0.01)
Rheumatoid arthritis	2 (0.01)	1 (0.01)
Seizure	3 (0.015)	2 (0.02)
Thrombocytopenia	2 (0.01)	1 (0.01)
Uveitis	2 (0.01)	2 (0.02)

Source: Source: EUA 28237 Amendment 15, ADAE dataset generated using MAED.
N=number of subjects in cohort

Of the 25 PIMMCs in the NVX-CoV2373 arm, 12 events reported by 11 participants were considered related to vaccination by the investigator, including uveitis (n=3); neuropathy peripheral, rheumatoid arthritis (n=2 each); and alopecia areata, Basedow's disease, Bell's palsy, psoriasis, and thrombocytopenia (n=1 each).); and). In the placebo arm, 2 events reported by 2 participants were considered related to vaccination by the investigator, including peripheral neuropathy and seizure. The following are descriptions of minor imbalances, related events, or PIMMCs of specific clinical interest reported by multiple participants:

- Two events of Basedow's disease and 1 event of autoimmune thyroiditis were reported in the NVX-CoV2373 arm compared to 1 event of autoimmune thyroiditis in the placebo arm. Although 1 case of Basedow's disease was considered related by the investigator, all participants in the NVX-CoV2373 arm had evidence of thyroid antibodies in baseline study laboratories, indicating that the conditions were pre-existing.
- Three events of Bell's palsy were reported in the NVX-CoV2373 arm compared to one event in the placebo arm. One event was reported 25 days following Dose 2 of NVX-CoV2373 and was considered related by the investigator and Sponsor. The remaining 2 events in the NVX-CoV2373 arm were reported 175 and 144 days post-Dose 2, respectively, and 1 event

was attributed to herpes labialis. One event of Bell's palsy was reported in the placebo arm 29 days post-Dose 2.

- Two events of thrombocytopenia were reported in the NVX-CoV2373 arm compared to 1 event in the placebo arm. One event was reported 13 days post-Dose 1 of NVX-CoV2372 in a participant hospitalized for surgical repair of a fracture with one abnormal platelet count (57 K/mm^3) that was preceded by normal values (229 K/mm^3) with a subsequent normal value on repeat 45 minutes later (307 K/mm^3). One event (platelet count 8 K/mm^3) was reported 32 days post-Dose 2 of NVX-CoV2373 in a participant on losartan with positive findings on a platelet antibody profile and positive losartan potassium IgG platelet antibody. The participant was treated with steroids and multiple platelet transfusions, and losartan was discontinued. The platelet count recovered to 122 K/mm^3 within one month but was noted to be decreased ~8 months later (82 K/mm^3). This case was considered related by the investigator, and as discussed in Section 6.2.5.5, FDA's opinion is that losartan-induced thrombocytopenia is a plausible alternative etiology for this event. One event in the placebo arm was reported 57 days post-Dose 2 and was associated with COVID-19.
- Events of peripheral neuropathy were reported by a higher proportion of participants in the placebo arm, including events with onset within 2 weeks of vaccination. Of the 3 events in the NVX-CoV2373 arm, 1 event involved bilateral numbness and paresthesia with onset the same day as Dose 1 and was ongoing and being treated with gabapentin as of the data extraction date, one event occurred 26 days post-Dose 1 and included bilateral upper and lower weakness and neuropathy, with a normal lumbar puncture and electromyelogram, and the remaining event was reported 1 day post-Dose 2 (no information on the details of this case were provided). The latter 2 events were considered related by the investigator. Of the 3 events in the placebo arm, the time to onset was between 8 and 26 days following the most recent placebo dose.
- Events of uveitis (including terms of uveitis, iritis, and iridocyclitis) were reported by a higher proportion of participants in the placebo arm, including events with onset within 2 months of vaccination. Three participants in the placebo arm reported events of uveitis 6, 21, and 50 days following the most recent placebo dose; 2 of whom had an apparent history of uveitis based on the verbatim terms ("recurrent" and "worsening"). Three participants in the NVX-CoV2373 arm reported 5 events of uveitis. One NVX-CoV2373 recipient had the onset of left-sided panuveitis 15 days post-Dose 1 of NVX-CoV2373; ophthalmologic exam revealed chronic changes that were thought to have preceded vaccination and he was treated with antivirals for presumed herpetic disease as well as steroids, after which his condition resolved. Attribution of this case is confounded by a potential infectious etiology and chronic ocular changes that may have preceded onset of symptoms, although the close temporal relationship to vaccination precludes exclusion of NVX-Co2373 as a contributor. One participant with a history of iritis reported right eye panuveitis and iritis 7 days post-Dose 1 of NVX-CoV2373 that resolved after initiation of steroids, but then recurred 16 days post-Dose 2. An extensive workup was unrevealing, and the symptoms resolved after a second course of steroids. Both cases of uveitis in the NVX-CoV2373 arm were considered related by the investigator. An additional case of iridocyclitis (bilateral anterior uveitis) was reported 18 days post-Dose 2 of NVX-CoV2373; however, this case did not meet protocol-defined criteria for a PIMMC based on the coding of the event term and was therefore not included in case counts. This 36-year-old male participant had a history of immune thrombocytopenic purpura and a family history of autoimmune disease; he was diagnosed with anterior uveitis with positive beta-2 microglobulin in the urine and evidence of acute kidney injury concerning for tubular intestinal nephritis with uveitis (TINU), although review of prior

creatinine laboratories did show previously elevated values. After treatment with steroids, the uveitis resolved. In an aggregated analysis of cases of events within 28 days of any dose, (including 26,151 NVX-CoV2373 recipients and 25,145 placebo recipients in both the pre- and post-crossover periods), events of uveitis (iritis, uveitis, iridocyclitis) were reported by 3 participants after NVX-CoV2373 (0.01%) and 2 participants after placebo (0.01%). All events were non-serious. One participant had onset of uveitis after Dose 1 of NVX-CoV2373 which resolved and then recurred following Dose 2. The two placebo recipients with events appeared to have had a previous history of uveitis compared to one participant who received NVX-CoV2373. Currently available information on uveitis is insufficient to determine a causal relationship with the vaccine, although the lack of previous history of uveitis and recurrence after a second dose in the NVX-CoV2373 arm is notable.

- Remaining events in the NVX-CoV2373 arm considered related by the investigator included alopecia areata 41 days post-Dose 2, without a specific alternative etiology, which was ongoing and resolving; worsening of pre-existing psoriasis 8 days post-Dose 1; and 2 events of seronegative rheumatoid arthritis with onset 1- and 3-days post-Dose 2, respectively, both of which occurred in participants with prior history of joint pain. The onset of symptoms in temporal relationship to vaccination may suggest an inflammatory response manifesting as persistent joint pain, although the prior history of joint pain may also suggest an exacerbation of an underlying condition either precipitated by or unrelated to vaccination.

In the post-crossover period through September 27, 2021, a total of 20 PIMMCs were reported by 6 (<0.1%) participants who crossed over to receive NVX-CoV2373 and 14 (<0.1%) participants who crossed over to receive placebo.

Table 20. Potential Immune-Mediated Medical Conditions Reported in the Post-Crossover Period, Study 301

Preferred Term	NVX-CoV2373 N=6416 Number of Subjects (%)	Placebo N=15298 Number of Subjects (%)
Ankylosing spondylitis	0 (0)	2 (0.013)
Bell's palsy	1 (0.016)	2 (0.013)
Dermatitis herpetiformis	0 (0)	1 (0.007)
Neuropathy peripheral	0 (0)	1 (0.007)
Polymyalgia rheumatica	0 (0)	1 (0.007)
Psoriasis	1 (0.016)	0 (0)
Rheumatoid arthritis	2 (0.031)	1 (0.007)
Seizure	1 (0.016)	1 (0.007)
Systemic lupus erythematosus	0 (0)	1 (0.007)
Thrombocytopenia	0 (0)	2 (0.013)
Type 1 diabetes mellitus	0 (0)	1 (0.007)
Vitiligo	1 (0.016)	1 (0.007)

Source: Source: EUA 28237 Amendment 15, ADAE dataset generated using MAED.
Abbreviation: PIMMC=Potential Immune-Mediated Medical Condition.
N=number of subjects in cohort.

Of the 20 PIMMCs, 2 were considered related by the investigator, including worsening of pre-existing dermatitis herpetiformis 85 days after the last dose of NVX-CoV2373 in the pre-crossover period and 1 day after placebo in the post-crossover period and vitiligo 26 days after the last dose of NVX-CoV2373 in the post-crossover period, confounded by administration of Pfizer COVID-19 vaccine 10 days prior to onset of symptoms. Events reported by multiple participants included 2 events of ankylosing spondylitis (72 and 88 days after the last dose of

NVX-CoV2373 administered in the pre-crossover period) and 16 and 11 days after the first dose of placebo in the post-crossover period, respectively, 3 events of Bell's palsy reported 20, 88, 200, and 221 days after the last dose of NVX-CoV2373, and 2 events of thrombocytopenia, both of which occurred >60 days following the most recent dose of NVX-CoV2373 in participants with multiple co-morbidities, including alcohol abuse and liver disease.

Additional safety data provided at FDA's request in a dataset with an extraction date of February 17, 2022, identified an additional 2 participants with PIMMCs in the pre-crossover period, including an event of polymyalgia rheumatica in the NVX-CoV2373 arm and an event of coeliac disease in the placebo arm. In the post-crossover period, 8 additional PIMMCs were reported by 8 participants, including rheumatoid arthritis and seizures (n=2 each); psoriatic arthropathy, systemic lupus erythematosus, scleroderma, and lichen planus (n=1 each). Only the event of scleroderma, reported 129 days after the last dose of NVX-CoV2373, was considered related by the investigator. This participant presented with myalgia and arthralgia and was diagnosed based on laboratory testing.

Cumulatively, in all 26,151 participants who received NVX-CoV2373 in the pre- and post-crossover periods, rheumatoid arthritis was the most commonly reported PIMMC following NVX-CoV2373 (n=7). There was no specific trend of temporality, with time to onset of events at 1, 3, 11, 92, 106, 149, 286, and 299 days after the most recent dose of NVX-CoV2373. In the absence of a long-term placebo comparator, it is uncertain whether this represents an excess of cases or the expected background rate of a common medical condition in the study population. Additionally, there were three events of uveitis/iridocyclitis with onset within 21 days of NVX-CoV2373, including one case of suspected TINU and one event that recurred upon re-challenge with Dose 2 of NVX-CoV2373. Although there was no imbalance in cases in the placebo-controlled pre-crossover period, FDA considers this cluster of similar events of uveitis with no potential alternative etiology, close temporal association to vaccination, and biologic plausibility for a potential autoimmune mechanism, to be possibly related to NVX-CoV2373, although the available information is insufficient to conclusively determine a causal relationship with the vaccine. Surveillance for further evaluation of uveitis events should be conducted with deployment of the vaccine into larger populations.

In summary, there were overall few events of PIMMCs, no imbalances noted in the placebo-controlled period, with generally comparable types of events and time to onset. In the absence of a longer term, placebo-controlled safety data collection period, it is difficult to discern background rates of relatively common medical conditions (e.g., rheumatoid arthritis) from potentially immune-mediated events related to vaccination with a long latency. Some PIMMCs were reported in closer temporal association to vaccination and with no clear alternative etiology identified (including Bell's palsy and peripheral neuropathy), and for these events a relationship to NVX-CoV2373 cannot be definitively excluded, although no imbalances were noted overall. Other than events of uveitis described above, there was no pattern of events to suggest a specific causal association between vaccine and a particular autoimmune spectrum of disease.

Selected Safety Analyses

The following section includes analyses of medical concepts for which imbalances were identified as well as search results from selected broad and narrow Standardized MedDRA Queries (SMQs) using FDA-developed software to evaluate unsolicited adverse events of clinical interest by searching PTs that could together represent various medical concepts.

Myocarditis/Pericarditis

Of particular interest were events of myocarditis and pericarditis. Postmarketing data from individuals receiving mRNA vaccines have demonstrated increased risks of myocarditis and pericarditis, particularly within 7 days following the second primary series dose. The observed risk has been highest in adolescent and young adult males. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms, although information is not yet available about potential long-term sequelae. The Spike protein antigen can induce antibodies to SARS-CoV-2 spike glycoproteins that cross-react with myocardial contractile proteins, including myocardial α-myosin heavy chain (Vojdani and Kharrazian, 2020). It has been postulated that the effect of these antibodies, influenced by hormonal differences, immune–genetic background, age, and sex are potential mechanisms of myocardial injury associated with SARS-CoV-2 infection or COVID-19 vaccination (Heymans and Cooper, 2022).

In the post-crossover period, events consistent with myocarditis and/or pericarditis were reported by 2 participants after NVX-CoV2373 (0.01%) and no participants after placebo, both of which had onset within 28 days of vaccination. One serious event was reported by a 67 year-old male 28 days after Dose 1 of NVX-CoV2373 (Dose 3 in study), associated with concomitant COVID-19, and 1 non-serious event was reported by a 20-year old male 10 days after Dose 1 of NVX-CoV2373 (Dose 3 of study).

Over the course of the clinical development program, events clinically consistent with myocarditis and pericarditis within 28 days of vaccination were identified in Studies 301 and 302, including in the adolescent expansion of" and booster dose amendment to Study 301. Therefore, an evaluation of cases of myocarditis and pericarditis was undertaken, incorporating data from across the clinical development program to provide the most robust assessment. Including participants in the adolescent and booster substudies of 301, 2 additional events were identified, including myocarditis reported by a 16 year-old adolescent (vaccine not authorized in this age group) 2 days after Dose 2 of NVX-CoV2373 (Dose 4 in study) and a 28 year-old male participant 3 days after a booster dose of NVX-CoV2373 (booster dose not authorized). Both of these events were serious. Including Study 302, 2 additional events were identified, including a 19 year-old with myocarditis 2 days after Dose 2 of NVX-CoV2373 and a 60 year-old with pericarditis 8 days after Dose 1 of NVX-CoV2373 (Dose 4 of study). In total, 6 cases of myocarditis and/or pericarditis were reported among approximately 42,000 participants ages 12 years or older who received NVX-CoV2373, including 5 participants with events occurring within 10 days following vaccination. Table 21 describes the 6 cases occurring after NVX-CoV2373. No cases of myocarditis or pericarditis were reported within 28 days following placebo.

Table 21. Myocarditis and/or Pericarditis Cases (in order of time to onset from vaccination) through 28 days after NVX-CoV2373 or Placebo

Study	Age/ Sex	Preferred Term	Dose Number, Days to Onset	Comments	Seriousness/Outcome	FDA Opinion
301	16/M	Myocarditis	NVX-CoV2373 CO Dose 2, 2 days	Preceding nonspecific viral illness and concomitant methylphenidate use. (Peak troponin ~32,000 ng/L).	Serious event. Hospitalized 4 days and treated with IVIG. Event recovered/resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine.
302	19/M	Myocarditis	NVX-CoV2373 Dose 2, 2 days	MRI consistent with myocarditis (peak troponin ~7,800 ng/L) Pharyngitis and lymphadenopathy 11 days later.	Serious event. Hospitalized 5 days. Event resolved after approximately 1 month.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine.
301	28/M	Non-ST elevation MI Initial report: atypical chest pain	NVX-CoV2373 Booster, 3 days	Adverse event described as acute MI but myocarditis in differential, with chest pain and elevated troponin (~300 ng/L). Unclear rationale for diagnosis of non-ST-elevation myocardial infarction versus myocarditis. A cardiac MRI obtained 5 months after the event was reported to show normal function and no stigmata of myocarditis.	Serious event. Hospitalized 2 days. Event recovered/ resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine. The long interval between the event and the follow-up MRI is not sufficient to exclude myocarditis.
302	60/F	Pericarditis	NVX-CoV2373 CO Dose 1, 8 days	With fever, elevated WCC and neutrophils, ECG consistent with pericarditis. Troponin normal.	Serious event. Hospitalized 2 days. Event recovered/ resolved.	Temporal relationship and lack of clear alternative etiology supports a concern for causal relationship to vaccine.

Study	Age/ Sex	Preferred Term	Dose Number, Days to Onset	Comments	Seriousness/Outcome	FDA Opinion
301	20/M	Pericarditis and myocarditis	NVX-CoV2373 CO Dose 1, 10 days	History of sore throat and fever 8 days prior to events, with exposure to streptococcal pharyngitis, and elevated anti streptolysin O titers. Troponin normal.	Non-serious event. Participant was not hospitalized. Second CO dose not administered. Participant lost to follow-up.	Although temporally related to vaccination, ARF and nonrheumatic streptococcal myocarditis are also plausible alternative etiologies.
301	67/M	Myocarditis	NVX-CoV2373 Dose 1, 28 days	Concomitant COVID-19 infection and acute kidney injury. Maximum troponin: 5329 ng/L.	Serious event. Hospitalized for 5 days. Second NVX-CoV2373 dose not administered. Event resolved with sequelae.	Relatively longer latency and diagnosis of COVID-19 support an alternative etiology, although association with vaccine cannot be definitively excluded.

Source: EUA 28237 Amendment 20, May 2, 2022, Table 1.
Abbreviations: ARF=acute rheumatic fever; CO=crossover; COVID-19=coronavirus disease-2019; ECG=electrocardiogram; MI=myocardial infarction; NA=not applicable (non-serious event); WCC=white cell count.

In summary, these events are concerning for a causal association between NVX-CoV2373 and myocarditis/pericarditis for the following reasons: 1) five events were reported within 10 days of vaccination, 2) only 1 event had a clearly identified alternative etiology (COVID-19) strongly associated with myocarditis, and some of the other events had only circumstantial evidence of potentially plausible alternative etiologies, and 3) four of the events occurred in young men, a subject population known to be at higher risk for mRNA COVID-19 vaccine-associated myocarditis. Additionally, identification of multiple potential vaccine-associated cases in a premarket safety database of ~42,000 vaccine recipients raises concern that if causally associated, the risk of myocarditis following NVX-CoV2373 could be higher than reported during post-authorization use of mRNA COVID-19 vaccines (for which no cases were identified in pre-authorization evaluation). Surveillance for further evaluation of events of myocarditis and pericarditis should be conducted with deployment of the vaccine into larger populations.

All Cardiac Events

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events in the Cardiac disorders SOC was comparable across the treatment arms (0.3% in each). Of the 76 events reported in the NVX-CoV2373arm, 40 (51%) were serious. Of the 31 events reported in the placebo arm, 17 (55%) were serious. The proportion of participants reporting each PT in the Cardiac disorders SOC was comparable across the treatment arms and the time to onset of events was also generally comparable across the treatment arms. A total of 10 fatal cardiac events were reported, including 4 (3 cardiac arrests and 1 myocardial infarction) in the placebo arm (0.04%) and 6 (5 cardiac arrests and 1 myocardial infarction) in the NVX-CoV2373 arm (0.03%). The time to onset of the fatal events was 6, 7, 8, and 14 days after the last dose of placebo and 12, 21, 23, 40, 58, and 64 days after the last dose of NVX-CoV2373. A total of 3 events in the NVX-CoV2373 arm (arrhythmia, tachycardia, and sinus bradycardia) and 2 events in the placebo arm (myocarditis and myocardial infarction) were considered related by the investigator.

A search for events with PTs consistent with the medical concept of myocardial infarction (myocardial infarction, acute coronary syndrome, and coronary artery occlusion), myocarditis, and cardiac arrest yielded 15 events in 15 participants in the NVX-CoV2373 arm (0.08%) and 11 events in 11 participants in the placebo arm (0.1%). The time to onset for the events in the placebo arm was within 30 days (n=8), 31-60 days (n=1), and 60-90 days (n=2). Of these events, 2 events in the placebo arm were considered related by the investigator (myocarditis and myocardial infarction). The time to onset for the events in the NVX-CoV2373 arm was within 30 days (n=7), 31-60 days (n=5), and 61-90 days (n=2), and >91 days (n=1). The time to onset for the events in the placebo arm was 30 days (n=8), 31-60 days (n=1), and 61-90 days (n=2).

The following SMQs were also used to assess for imbalances across the treatment arms in the pre-crossover period: Ischemic heart disease, Cardiac failure, Cardiac arrhythmias, and Cardiomyopathy.

The proportion of participants with events retrieved using the SMQ Ischemic heart disease (broad and narrow) was comparable between the NVX-CoV2373 (0.1%) and placebo (0.1%) arms. Of the 16 events in 15 participants in the NVX-CoV2373 arm, 4 (25%) had onset within 2 weeks of the most recent vaccination. Of the 8 events in 7 participants in the placebo arm, 6 (75%) had onset within about 2 weeks of vaccination. Serious adverse events with onset within 7 days of vaccination are described in detail in Section 6.2.5.7.

Table 22. Events from Standard MedDRA Query *Ischemic Heart Disease*, Pre-Crossover Period, Scope: Narrow + Broad, Safety Analysis Set, Study 301

MedDRA Preferred Term	NVX-CoV2373 N=19735	Placebo N=9847
Total, n (%)	15 (0.1)	7 (0.1)
Acute myocardial infarction, n (%)	2 (0.01)	4 (0.04)
Angina pectoris, n (%)	2 (0.01)	0 (0.00)
Coronary artery disease, n (%)	3 (0.02)	1 (0.01)
Myocardial infarction, n (%)	5 (0.03)	3 (0.03)
Acute coronary syndrome, n (%)	1 (0.01)	0 (0.00)
Coronary artery occlusion, n (%)	1 (0.01)	0 (0.00)
Stress cardiomyopathy, n (%)	1 (0.01)	0 (0.00)
Ischemic cardiomyopathy, n (%)	1 (0.01)	0 (0.00)

Source: Source: EUA 28237 Amendment 15, ADAE2 dataset generated using MAED.
Abbreviations: CI=confidence interval; SMQ=Standardized Medical Dictionary for Regulatory Activities Query.
n=number of subjects with indicated parameter; N=number of subjects in cohort.

The proportion of participants with events retrieved using the SMQ Cardiomyopathy (broad and narrow) was comparable between the NVX-CoV2373 (0.5%) and placebo (0.4%) arms. In general, the proportion of participants reporting each type of event was comparable across treatment groups. However, terms specific for events of cardiomyopathy or cardiac failure were reported by 9 participants in the NVX-CoV2373 arm (0.05%) compared to 2 participants in the placebo arm (0.02%). The time to onset was within ~2 weeks for 5 events (56%) in the NVX-CoV2373 arm and within 2 weeks for 1 event (50%) in the placebo arm. Both events in the placebo arm and 6 of 9 events in the NVX-CoV2373 arm were serious, and none of the events were considered related. All participants in the NVX-CoV2373 arm with events of cardiomyopathy or cardiac failure had a history of previous cardiac disease, obesity, or other co-morbidities, with the exception of one participant with a non-serious event of stress cardiomyopathy who had no medical history reported.

The proportion of participants with events retrieved using the SMQ Cardiac failure (broad and narrow), was slightly higher in the NVX-CoV2373 arm (0.2%) compared to the placebo arm (0.1%). However, terms specific for events of cardiac failure were reported by 8 participants in the NVX-CoV2373 arm (0.04%) compared to 1 participant in the placebo arm (0.01%). The onset of the event reported in the placebo arm was 8 days post-Dose 2 of placebo. Of the 8 cases in the NVX-CoV2373 arm, 6 occurred in participants with a history of congestive heart failure, 6 had time to onset within 21 days of the most recent NVX-CoV2373 dose, 6 were serious, and none were considered related. All participants had co-morbidities, including obesity.

The proportion of participants with events retrieved using the SMQ Cardiac arrythmia (broad and narrow) was comparable between the NVX-CoV2373 (0.3%) and placebo (0.3%) arms. Events of atrial fibrillation and increased heart rate were reported by a slightly higher proportion of participants in the NVX-CoV2373 arm compared to the placebo arm, although the differences were small. Most events of atrial fibrillation were >2 weeks following vaccination and most events of heart rate increased were the day of or shortly following vaccination, which may reflect reactogenicity.

In the post-crossover period through September 27, 2021, a total of 53/21,714 (0.2%) participants who received NVX-CoV2373 either in the pre-or post-crossover period experienced 61 adverse events in the SOC Cardiac disorders. Of the 61 events, 40 (66%) were serious, including 3 fatal events (1 event each of cardiac arrest and myocardial infarction, and 1 event of

alcoholic cardiomyopathy). The time to onset of the fatal events from the most recent NVX-CoV2373 dose was 8 days for an event of cardiac arrest and >80 days for the remaining events. Three events (myocarditis, pericarditis, and bradycardia) were considered related by the investigator. Although the arm that crossed over to receive placebo is not a true comparator, given the previous exposure to NVX-CoV2373, imbalances during the post-crossover period that may reflect short-term risk interval windows were assessed. A total of 6/6,416 (0.1%) participants who crossed over to receive NVX-CoV2373 experienced events consistent with myocardial infarction compared to 7/15,298 (0.05%) participants who crossed over to receive placebo. Events in the arm that crossed over to NVX-CoV2373 had time to onset of <30 days (n=3), 31-60 days (n=1), and >90 days (n=2), compared to events in the arm that crossed over to receive placebo, which had time to onset of <30 days (n=4), 31-60 days (n=2), and >90 days (n=1), relative to the most recent placebo dose. The time to onset is comparably distributed across the treatment arms, suggesting that there is no increase in events occurring in the risk window immediately following vaccination; however, varying lengths of follow up post-crossover may limit a full assessment of temporal clustering.

A review of cases retrieved using the SMQs Ischemic heart disease, Cardiac failure, Cardiac arrhythmias, and Cardiomyopathy did not reveal additional imbalances between participants who crossed over to receive NVX-CoV2373 versus placebo.

Due to imbalances noted above, an aggregated analysis of cases of events within 28 days of any dose through the September 27, 2021 data cutoff (including 26,151 NVX-CoV2373 recipients and 25,145 placebo recipients in both the pre- and post-crossover periods), was conducted for events of cardiomyopathy or cardiac failure. Events were reported by 8 participants after NVX-CoV2373 (0.03%) and 1 participant after placebo (<0.01%). All events were serious. Additionally, an event of congestive cardiac failure was reported after NVX-CoV2373 by a participant who was excluded from the safety analysis set (enrolled at Site 151). Currently available information on cardiomyopathy or cardiac failure is insufficient to determine a causal relationship with the vaccine; however, this imbalance is notable. Data provided at FDA's request in a dataset with a cutoff date of February 17, 2022, was used to assess additionally accrued AEs of cardiac events in the post-crossover period. A total of 39 additional events in the SOC Cardiac disorders were identified with onset after September 27, 2021, all of which had occurred 140 days or more since the most recent dose of NVX-CoV2373. Incorporating these additional events resulted in a total of 10/6,416 (0.16%) participants who crossed over to receive NVX-CoV2373 and who experienced events consistent with myocardial infarction (myocardial infarction, coronary artery occlusion, cardiac arrest, and acute coronary syndrome) compared to 14/15,298 (0.09%) participants who crossed over to receive placebo. In an expanded analysis including additional events that may not reflect acute myocardial infarction (angina pectoris, angina unstable, atherosclerosis, coronary artery disease, and coronary artery stenosis), events were reported by 19/6,146 (0.3%) participants who crossed over to receive NVX-CoV2373 compared to 21/15,298 (0.14%) of participants who crossed over to receive placebo. The time to onset was comparably distributed among the treatment arms, with 50% of events within 28 days of the crossover placebo dose and 32% of events within 28 days of the crossover NXV-CoV2373 dose.

The February 17, 2022, updated data reflected a cumulative total of 51 participants who received NVX-CoV2373 in the pre- or post-crossover period (n=26,151) and reported events consistent with myocardial infarction or coronary artery disease (n=40), myocarditis (n=3), pericarditis (n=1), and cardiac arrest (n=7). To assess for potential long-term cardiac events, events consistent with the medical concept of cardiomyopathy and cardiac failure were

analyzed. A total of 22 participants reported 27 AEs, none of which were considered related, without temporal clustering noted. With the exception of stress cardiomyopathy, all participants with these events had risk factors for cardiac disease (e.g., obesity, pre-existing heart disease).

In summary, cardiac events, including fatal events of cardiac arrest and myocardial infarction, were reported with close temporal relationship to NVX-CoV2373; however, the proportions of participants with fatal, serious, and ischemic cardiac events were generally balanced across the treatment arms for the blinded pre-crossover period, with comparable times to onset. As discussed in the Deaths section below, there was little to no information available on many of the cardiac deaths, precluding a full assessment of causality. Although it is possible that some cardiac events, including fatal events, were severe manifestations of undiagnosed myocarditis (see below), there is comparability across treatment arms in aggregate analyses of the type, severity, and temporality of cardiac events. Additionally, attribution of causality in many of the cardiac events is confounded by the presence of pre-existing conditions and risk factors.

Additionally, numerical imbalances were noted between the treatment arms with respect to events of cardiac failure and cardiomyopathy, including some events in close temporal proximity to vaccination. The available data do not allow for a conclusion of a causal relationship. Surveillance for further evaluation of events of cardiac failure and cardiomyopathy should be conducted with deployment of the vaccine into larger populations.

Hypersensitivity Reactions

In an aggregate assessment of cases within 7 days of any dose (including all 26,151 NVX-CoV2373 recipients and all 25,145 placebo recipients in both the pre- and post-crossover periods), hypersensitivity reactions (reported terms including urticaria, angioedema or swelling of the face, lips, ear, and/or eyelids, and hypersensitivity) occurred in 26 participants after NVX-CoV2373 (0.1%) and 8 participants after placebo (0.03%).

Among the 12 events of angioedema or swelling of the face, lips, ear, eyelids, one non-serious case of angioedema was accompanied by purpura, which occurred 1 day after NVX-CoV2373 and resolved within 3 days following treatment with dexamethasone, cetirizine, prednisone, and famotidine. One serious case of angioedema initially began as generalized urticaria in a 32-year-old woman 2 days after Dose 1 of NVX-CoV2373. The reaction progressed to angioedema of the lips and tingling of the tongue, for which she sought medical attention and was treated with epinephrine, corticosteroids, and antihistamines. This participant was evaluated as an outpatient by an allergist-immunologist, who did not consider the reaction to represent an IgE-mediated process (i.e., anaphylaxis) or a severe cutaneous drug reaction, but rather acute urticaria and dermatographism resulting from a combination of potential triggers, including an adjuvanted vaccine, nitrofurantoin (for an intercurrent urinary tract infection), perimenstrual hormone shifts, and ibuprofen. This event is also described in Table 24.

Hypertension

Due to multiple SAEs of hypertension reported in the NVX-CoV2373 arm, an analysis of hypertension events was conducted using the SMQ Hypertension to assess for imbalances in the treatment arms. In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Hypertension (narrow and broad) was comparable in the NVX-CoV2373 and placebo arms (0.6% in each). Of the 111 events in the NVX-CoV2373 arm, 29 (26%) had onset within 3 days of vaccination. Five events were serious (including hypertension [n=2] hypertensive crisis, hypertensive emergency, and hypertensive

urgency). The time to onset for serious events in the NVX-CoV2373 arm ranged from 11 to 90 days following the most recent dose of NVX-CoV2373. In the placebo arm, 3 events were considered related by the investigator, 1 event was serious, and 10 (17%) had onset within 3 days of vaccination. The SMQ Hypertension (broad) was used to retrieve events with onset through 3 and 7 days after the most recent dose, and no imbalances were observed at these time points. The majority of the participants in the NVX-CoV2373 and placebo arms with new onset hypertension were older and/or had obesity as a comorbidity.

In the post-crossover period through September 27, 2021, the proportion of participants reporting events in the SMQ Hypertension (narrow and broad) was comparable between participants who crossed over to receive NVX-CoV2373 or placebo (0.2% in each). Events with onset within 3 days of the most recent dose were reported by a higher proportion of participants who crossed over to receive placebo.

No pattern of severity, relatedness, or temporality was identified to suggest a possible association of NVX-CoV2373 with hypertensive events.

Biliary Events

Due to an observed imbalance in biliary events (specifically cholecystitis and cholelithiasis) observed in the pre-crossover period, the SMQ Biliary disorders was used to further analyze these events. Through September 27, 2021, the proportion of participants with events retrieved using this SMQ was higher in the NVX-CoV2373 arm (0.08%) compared to the placebo arm (0.04%) in the pre-crossover period. Events of cholecystitis (including acute and chronic) were reported by 10 participants (0.05%) in the NVX-CoV2373 arm compared to 1 participant in the placebo arm (0.01%). None of the events were considered related by the investigator. Of the 11 events, all were serious with the exception of 1 event in the NVX-CoV2373 arm. Of the 10 events in the NVX-CoV2373 arm, 5 (40%) had onset within 28 days of the most recent vaccination; the event in the placebo arm occurred 84 days after the most recent dose. The remaining events in the NVX-CoV2373 arm had time to onset ranging from 34 to 117 days. Most participants with these events were female, obese, and/or had a history of cholelithiasis.

In the post-crossover period through September 27, 2021, the proportion of participants with events retrieved using the SMQ Biliary disorders was higher in the NVX-CoV2373 arm (0.14%) compared to the placebo arm (0.03%). Events of cholecystitis (including acute and chronic) were reported by 8 participants (0.1%) who crossed over to receive NVX-CoV2373 compared to 3 participants who crossed over to receive placebo (0.02%). One event of chronic cholecystitis was considered related by the investigator, with onset 25 days post-Dose 2 of NVX-CoV2373. All events in both arms were serious. The time to onset following crossover placebo doses was 4, 26, and 66 days after the most recent dose, and time to onset following crossover NVX-CoV2373 doses was 21 to 130 days, with 1 event within 28 days of vaccination. All 11 participants with cholecystitis events had underlying risk factors for cholelithiasis, including overweight/obesity and biliary dyskinesia.

In an aggregated analysis of cases of acute cholecystitis events within 28 days of any dose, (including 26,151 Novavax COVID-19 Vaccine, Adjuvanted recipients and 25,145 placebo recipients in both the pre- and post-crossover periods), events were reported by 6 participants after NVX-CoV2373 (0.02%) and by 2 participants after placebo (0.01%). All events were serious. Currently available information on cholecystitis is insufficient to determine a causal

relationship with the vaccine; however, the imbalance in events with close temporal relationship to NVX-CoV2373 is notable.

In the pre-crossover period, events of cholelithiasis were reported by 7 participants (0.04%) in the NVX-CoV2373 arm compared to 2 participants in the placebo arm (0.02%). Two events in the NVX-CoV2373 arm were serious, and the remaining events were non-serious; none were considered related by the investigator. In the NVX-CoV2373 arm, the time to onset was within 28 days of the most recent vaccination for 5 events, with onset at 52 and 63 days for the remaining events. The events in the placebo arm occurred at 9 and 30 days after the most recent placebo dose. In the post-crossover period, events of cholelithiasis were reported by 1 participant who crossed over to receive NVX-CoV2373 115 days post-crossover Dose 2 and 2 participants who crossed over to receive placebo at 9 and 25 days after the last dose of placebo.

Cumulatively, through the February 17, 2022, data extraction date, a total of 38 of the 26,151 participants (0.1%) who received NVX-CoV2373 in the pre- or post-crossover periods reported events consistent with cholelithiasis and cholecystitis, and 24 of these events were cholecystitis.

In summary, although small imbalances in events of cholelithiasis were seen in the pre-crossover placebo-controlled period of the study, there is no clear mechanism to support a causal association, and the temporal pattern of events was similar in both treatment arms. An imbalance in cholecystitis events was noted in both the pre- and post-crossover period, with some clustering of events in temporal relationship to vaccination in participants with risk factors for gallstones. The available data do not allow for a conclusion of a causal relationship, nor do they allow for a definitive conclusion against the vaccine as a contributing factor. Surveillance for further evaluation of hepatobiliary events should be conducted with deployment of the vaccine into larger populations.

Neurovascular Events

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Central nervous system disorders (broad) were comparable across the treatment arms. However, an imbalance was observed in the proportion of participants with adverse events consistent with stroke in the NVX-CoV2373 arm (n=11; 0.06%) compared to the placebo arm (n=2; 0.02%). Events in the NVX-CoV2373 arm included cerebrovascular accident (CVA; n=7), ischemic stroke (n=1), cerebral infarction (n=1), and transient ischemic attack (n=2) and occurred in individuals between the ages of 49 and 74 years. One event of CVA was reported after a subject withdrew from the study but was recorded; this case is included in this analysis for completeness. One event of CVA 49 days after the most recent NVX-CoV2373 was fatal. The range of time to onset for the remaining events was between 11 and 84 days, including 3 events within 15 days of the most recent dose of NVX-CoV2373, 5 events between 32 and 49 days of the most recent dose of NVX-CoV2373, and 3 events occurring 77 days or more following the most recent dose of NVX-CoV2373. Of the 11 participants, 2 had potential alternative etiologies, including 1 participant with atrial fibrillation and a computed tomography angiography (CTA) with/without contrast of the head that was negative for stroke and one participant who was admitted with stroke-like symptoms but discharged home without intervention with a referral to neurology for a “pinched nerve.” With 1 exception, all participants had co-morbidities that may have increased the risk of stroke (e.g., hypertension, obesity). Events in the placebo arm included cerebellar infarction and transient

ischemic attack and occurred in participants 61 and 58 years of age, respectively, at 9 and 14 days after the most recent dose of placebo.

In the post-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Central nervous system disorders (broad) was higher in the participants who crossed over to receive placebo. A total of 5 participants who crossed over to receive placebo experienced adverse events consistent with the clinical concept of stroke, including transient ischemic attack (n=3), ischemic stroke, and CVA. These events occurred in participants 35 to 79 years of age, most of whom had co-morbidities that may have increased the risk of stroke (e.g., elderly, obesity). The range of time to onset was between 74 and 155 days following the most recent dose of NVX-CoV2373, with 3 of the 5 events occurring >140 days following vaccination.

Additional safety data provided at FDA's request with a data extraction date of February 17, 2022, added 1 event of CVA each in the NVX-CoV2373 and placebo arms in the pre-crossover period, with time to onset of 319 and 267 days following the most recent vaccination, respectively. In the post-crossover period, an additional 2 events were reported, including CVA and transient ischemic attack, with time to onset 142 and 299 days after the most recent dose of NVX-CoV2373, respectively. Cumulatively, a total of 19 events were reported following NVX-CoV2373 in the pre- and post-crossover periods (n=26,151), with time to onset <30 days (n=3), 31-60 days (n=5), 61- 90 days (n=4), 90-120 days (n=1), and >121 days (n=6). The outcome of these events was recovered with sequelae (n=6), recovered or recovering (n=11), and fatal (n=2, events with onset 155- and 49-days post-Dose 2 of NVX-CoV2373).

In summary, assessment of the numerical imbalance in neurovascular events the pre-crossover period is confounded by the presence of risk factors in the individual participants, the observation of events in close temporal relationship to vaccination in both treatment arms, no clear pattern in the time to onset of events to suggest a specific pathophysiologic mechanism for a causal relationship to NVX-CoV2373, and a lack of a similar imbalance noted in the post-crossover period. It is notable that several neurovascular events were associated with arterial wall defects, including two strokes associated with arterial dissections, including the carotid and right vertebral artery, one stroke with a possible dissection noted on imaging, and a fatal event of a traumatic rupture of a vertebral artery aneurysm (not included above as a stroke case).

Although the available data do not clearly demonstrate an association of neurovascular events with NVX-CoV2373, surveillance for further evaluation of thromboembolic and neurovascular events should be conducted with deployment of the vaccine into larger populations.

Guillain-Barre Syndrome/Neuropathy

As discussed in Section 7, 1 participant in Study 302 reported an event consistent with Guillain-Barre syndrome (GBS). No events of GBS were reported in Study 301; however, the SMQs Guillain-Barre syndrome, Peripheral neuropathy, and Demyelination were used to identify potential cases. In the pre-crossover period through September 27, 2021, the proportions of participants reporting events retrieved using the SMQs Guillain Barre syndrome and Peripheral neuropathy were comparable between the NVX-CoV2373 (0.2%) and placebo (0.3%) arms. No imbalances in specific event terms were noted. No events were retrieved using the SMQ Demyelination.

Events consistent with the medical concept of radiculopathy, neuropathy, or neuropathic pain were reported by 27 participants in the NVX-CoV2373 arm (0.1%) and 15 participants in the placebo arm (0.2%) in the pre-crossover period. There were no imbalances across the treatment arms with regard to each specific event. All of the events had onset within 28 days of the last NVX-CoV2373 or placebo dose; the time to onset was within 7 days of the most recent dose for 9 events (60%) in the placebo arm and 20 events (71%) in the NVX-CoV2373 arm.

In the post-crossover period through September 27, 2021, the proportion of participants reporting events retrieved using the Guillain Barre syndrome SMQ was comparable between participants who crossed over to receive placebo (0.3%) or NVX-CoV2373 (0.2%). No imbalances in specific event terms were noted. The proportion of participants reporting events retrieved using Peripheral neuropathy SMQ was numerically higher in participants who crossed over to receive NVX-CoV2373 (0.09%) compared to participants who crossed over to receive placebo (0.05%). Only 1 event was retrieved using the Demyelination SMQ, in a participant who crossed over to receive placebo.

Events consistent with the medical concept of radiculopathy, neuropathy, or neuropathic pain were reported by 6 participants who crossed over to receive placebo (0.04%) and 3 who crossed over to receive NVX-CoV2373 (0.05%). The time to onset of events relative to the last dose of NVX-CoV2373 (either in the pre- or post-crossover period) was >60 days for 6 events and 1, 4, and 22 days for the remaining events. Two events of clinical interest were reported, including immune-mediated neuropathy and neuralgic amyotrophy. The event of immune-mediated neuropathy was reported 68 days post-Dose 2 of NVX-CoV2373 in a 33-year old woman. Neurologic symptoms included tingling in the right arm and leg and weakness in the right arm. This event was considered related to vaccination by the investigator, and the participant was discontinued from vaccination. There is insufficient information to inform a causality assessment and the rationale for the diagnosis of immune-mediated neuropathy is not provided. The event of neuralgic amyotrophy (Parsonage-Turner syndrome) in a 57-year old male participant with a history of right upper extremity Parsonage Turner syndrome (2008-2009) and right frozen shoulder was severe and considered related by the investigator. Four days after the first post-crossover dose of NVX-CoV2373 administered into the right arm, the participant reported neck and left arm pain which subsequently resolved but then recurred 6 weeks later. A magnetic resonance imaging (MRI) scan of the cervical spine showed progressive multilevel degenerative disc disease, spinal stenosis, and left and right foraminal stenosis. Subsequent workup approximately 3 months after the initial presentation included an electromyogram which suggested branchial neuritis and an MRI of the left brachial plexus which was compatible with mild acute or chronic brachial plexopathy. This event was ongoing at the time of the report. The prior history of Parsonage-Turner syndrome and vaccination into the contralateral arm suggest a plausible alternative etiology.

Additional data provided at FDA's request in a dataset with extraction date of February 17, 2022, did not identify any additional participants diagnosed with GBS.

Embolic and Thrombotic Events

In the context of neurovascular and cardiac events described above, an overall assessment of thrombotic and embolic events was performed using the SMQ Embolic and Thrombotic Events to retrieve cases.

In the pre-crossover period through September 27, 2021, the proportion of participants with adverse events retrieved using the SMQ Embolic and Thrombotic Events (broad) was comparable between the NVX-CoV2373 arm (0.16%) and the placebo arm (0.14%). The proportion of participants with each event in the SMQ was comparable with the exception of an imbalance with respect to neurovascular events as described in detail above. Excluding cardiac and neurovascular events, a total of 10 participants in the NVX-CoV2373 arm (0.06%) reported 11 thrombotic and embolic events, including pulmonary embolism (n=4), deep vein thrombosis (n=3), thrombosis (n=2), mesenteric artery thrombosis, and peripheral arterial occlusive disease (n=1 each). A total of 5 participants in the placebo arm (0.06%) reported 6 events, including pulmonary embolism (n=2), deep vein thrombosis, embolism, peripheral arterial occlusive disease, and catheter site thrombosis (n=1 each). None of the events were considered related by the investigator. These events are summarized in Table 23.

Table 23. Non-Cardiac/Non-Neurovascular Embolic and Thrombotic Events Pre-Crossover Through September 27, 2021, Safety Analysis Set, Study 301

Pre-Crossover Treatment	Age/ Sex	Preferred Term	Risk Factors	Serious	Time to Onset (Days)	Comment
Placebo	72/F	Pulmonary embolism	Hypertension, obesity, diabetes mellitus	Yes	16 PD 1	Concomitant COVID-19
Placebo	59/M	Pulmonary embolism and deep vein thrombosis	Coronary artery disease, myocardial infarction, obesity	Yes	30 PD 2	Prolonged inactivity prior to events
Placebo	62/M	Catheter site thrombosis	Hypertension and sacral osteomyelitis	Yes	32 PD 2	Peripherally inserted central catheter clot
Placebo	57/F	Embolism	Breast cancer, obesity	Yes	74 PD 1	Limited information available on site of thrombus
Placebo	75/M	Peripheral arterial occlusive disease	Peripheral arterial disease, diabetes mellitus, hypertension, coronary artery disease	Yes	74 PD 2	Occlusion of prior fem-fem graft
NVX-CoV2373	83/M	Pulmonary embolism and Deep vein thrombosis	Myocardial infarction, chronic bilateral lower extremity DVT with inferior vena cava filter placement, hypertension, Type 2 diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, Alzheimer's disease, and dyslipidemia	Yes	3 PD 1	Computed tomography angiography of the chest with contrast showed right lower lobar and segmental pulmonary emboli, duplex ultrasound of the bilateral lower extremities showed bilateral DVTs, and echocardiogram revealed an ejection fraction of 35-45% and severely dilated left atrium. Acute on chronic decompensated systolic congestive heart failure exacerbation, acute respiratory failure, and pulmonary embolism were diagnosed. presented with respiratory distress and peripheral edema 2 days post-Dose 1 of NVX-CoV2373. The platelet count was 134 x 10^3/µL.
NVX-CoV2373	54/M	Pulmonary embolism	Primary thrombophilia, recurrent DVT left leg and recurrent pulmonary embolism, morbid obesity, lower extremity stent placement	Yes	5 PD 1	Presented with left leg and hip pain and diagnosed with deep vein thrombosis and pulmonary embolism.

Pre-Crossover Treatment	Age/ Sex	Preferred Term	Risk Factors	Serious	Time to Onset (Days)	Comment
NVX-CoV2373	65/M	Mesenteric artery thrombosis	Admitted with perforated appendicitis and non-occlusive thrombus in superior mesenteric artery noted on CT scan	No	13 PD 1	Unclear whether the clot was pre-existing, related to acute abdominal infection, or spontaneous and coincidental
NVX-CoV2373	59/M	Deep vein thrombosis	Alcohol abuse, deep vein thrombosis, drug abuse, hyperlipidemia, hypertension, obesity, diabetes mellitus	No	15 PD 1	No narrative available
NVX-CoV2373	61/M	Peripheral arterial occlusive disease	Morbid obesity	No	15 PD 2	No narrative available
NVX-CoV2373	58/M	Thrombosis	Hypertension, overweight	No	16 PD 1	No narrative available
NVX-CoV2373	71/F	Pulmonary embolism	Deep vein thrombosis, obesity	Yes	20 PD 1	COVID-19 11 days prior to onset provides plausible alternative etiology
NVX-CoV2373	58/M	Thrombosis	Atrial fibrillation	No	29 PD 2	Blood clot in knee, no narrative available
NVX-CoV2373	60/F	Deep vein thrombosis	Obesity	No	59 PD 2	No narrative available
NVX-CoV2373	42/F	Pulmonary embolism	Cerebral venous sinus thrombosis, obesity	Yes	152 PD 2	Deep vein thrombosis also present

Source: FDA-generated analysis from September 27, 2021, ADAE dataset.
Abbreviations: COVID-19=coronavirus disease-2019; CT=computed tomography; DVT=deep vein thrombosis; F=female; M=male; PD=post-dose.

A total of 7 participants in the NVX-CoV2373 arm experienced thrombotic/embolic events within 21 days of the most recent NVX-CoV2373 dose, 2 of whom had plausible alternative etiologies (appendicitis associated with mesenteric artery thrombosis and COVID-19 associated with pulmonary embolism). Only one participant in the placebo arm had onset of thrombotic/embolic events within 21 days of the most recent dose, with a clear alternative etiology of COVID-19.

In the post-crossover period through September 27, 2021, a total of 9 participants who crossed over to receive placebo (0.06%) reported ten non-cardiac, non-neurovascular events in the SMQ Embolic and Thrombotic Events, including pulmonary embolism (n=5), deep vein thrombosis (n=3), and peripheral arterial disease (n=2), 6 of which had onset within 2 weeks following the most recent crossover placebo dose (onset was 60 days or more following NVX-CoV2373 administered in the pre-crossover period). None of these events was considered related by the investigator. A total of 4 participants who crossed over to receive NVX-CoV2373 (0.06%) reported 4 events in the SMQ Embolic and Thrombotic Events, including pulmonary embolism (n=3) and portal vein thrombosis. Two events of pulmonary embolism (one of which was considered related by the investigator) and the event of portal vein thrombosis all had onset within 9 days of NVX-CoV2373, and the remaining event of pulmonary embolism occurred 110 days after NVX-CoV2373. The events of pulmonary embolism occurred in participants with risk factors (e.g., use of concomitant estrogen in one participant, obesity) at 7 and 9 days after the second crossover dose of NVX-CoV2373. The event of portal vein thrombosis was reported by a 77-year-old male with a history of hyperlipidemia, hypertension, allergies to influenza and pneumococcal vaccine, and transient ischemic attack who presented with ongoing fever and anemia (hemoglobin decreased to 9.5 g/dL from 14.0 g/dL), mildly elevated transaminases and bilirubin 9 days after the second post-crossover dose of NVX-CoV2373. A diagnosis of systemic inflammatory response was made. A right upper quadrant ultrasound showed hepatic steatosis versus fibrosis and hepatic cysts. It was reported that the systemic inflammatory response syndrome was likely secondary to bacterial versus rickettsial infection, although diagnostic testing did not reveal an etiology. Additional diagnoses during this stay included pan-diverticulosis, portal vein thrombosis, melena due to suspected gastrointestinal bleed (resolved), microcytic anemia due to suspected gastrointestinal bleed. There was an improvement in transaminitis over the course of the hospitalization and the participant was discharged home with anticoagulation. Attribution of causality for the event of portal vein thrombosis in this case is confounded by a lack of information on the presence of underlying hepatic disease or assessment of chronic versus acute portal vein thrombosis, as well as no clear alternative infectious etiology for the presenting complaint of fever.

In an aggregated analysis of cases of events within 28 days of any dose, (including 26,151 Novavax COVID-19 Vaccine, Adjuvanted recipients and 25,145 placebo recipients in both the pre- and post-crossover periods), events of non-cardiac, non-neurovascular thrombotic and embolic events were reported by 11 participants after NVX-CoV2373 (0.04%) and 6 participants after placebo (0.02%). Events following NVX-CoV2373 included pulmonary embolism (n=5), deep vein thrombosis and thrombosis (n=2), and portal vein thrombosis, mesenteric artery thrombosis, and peripheral arterial occlusive disease (n=1 each); 6 of the events were serious, including pulmonary embolism (n=5) and deep vein thrombosis (n= 1). Events following placebo included pulmonary embolism (n=3), and deep vein thrombosis and peripheral arterial occlusive disease (n=2 each), all of which were serious except deep vein thrombosis and peripheral arterial occlusive disease (n= 1 each).

Cumulatively, through the data extraction date of February 17, 2022, a total of 83 of the 26,151 participants (0.3%) who received NVX-CoV2373 in the pre-or post-crossover period reported

events captured by the SMQ Embolic and Thrombotic Events (narrow and broad). The most commonly reported events included events consistent with stroke (n=19; 0.1%), pulmonary embolism (n=18, 0.1%), myocardial infarction/acute myocardial infarction (n=24, 0.1%), and deep vein thrombosis (n=11, 0.05%). An imbalance in events of pulmonary embolism was noted for the post-crossover period (0.1% of participants who crossed over to receive NVX-CoV2373 compared to 0.05% of participants who crossed over to receive placebo). However, most events in both treatment arms had onset >90 days following the most recent dose, and the proportion of events with onset <2 weeks was comparable.

In summary, for non-cardiac, non-neurovascular events (Table 23), 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. Attribution of causality is confounded by the presence of the pre-existing conditions and risk factors. As such, data at this time are insufficient to conclude a causal relationship between the vaccine and thromboembolic events. As noted previously, surveillance for further evaluation of thromboembolic events, including cardiac and neurovascular events, should be conducted with deployment of the vaccine into larger populations.

6.2.5.5 Medically Attended Adverse Events

In the pre-crossover period through September 27, 2021, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms (5.8% and 0.5%, respectively, in the NVX-CoV2373 arm and 5.7% and 0.3%, respectively, in the placebo arm). In the pre-crossover period, the proportion of participants reporting each MAAE was comparable across the treatment arms, and no specific preferred term was reported by more than 0.3% of participants in the NVX-CoV2373 arm. The highest risk difference between treatment groups was for the events of vertigo (0.07% in the NVX-CoV2373 arm and 0.01% in the placebo arm) and oropharyngeal pain (0.07% in the NVX-CoV2373 arm and 0.01% in the placebo arm). There were no trends in the pre-crossover MAAE data that were not identified in review of the unsolicited safety data.

In the post-crossover period through September 27, 2021, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms (4.7% and 0.3%, respectively, in the NVX-CoV2373 arm and 4.0% and 0.2%, respectively, in the placebo arm). Excluding cases of COVID-19 and COVID-19 pneumonia, the highest risk difference between treatment groups was for the events of depression (0.1% in the participants who crossed over to receive NVX-CoV2373 and 0.06% in the participants who crossed over to receive placebo) and urinary tract infection (0.2% in the participants who crossed over to receive NVX-CoV2373 and 0.1% in the participants who crossed over to receive placebo). There were no trends in the post-crossover MAAE data that were not identified in review of the unsolicited safety data.

Through February 17, 2022, the proportions of participants reporting MAAEs and related MAAEs was comparable across the treatment arms in the pre-crossover period (6.1% and 0.5%, respectively, in the NVX-CoV2373 arm and 5.9% and 0.3%, respectively, in the placebo arm) and the post-crossover period (6.2% and 0.4%, respectively, in participants who crossed over to NVX-CoV2373 and 5.5% and 0.2%, respectively, in participants who crossed over to

placebo). There were no trends in the additional or cumulative pre- and post-crossover MAAE data that were not already identified in review of the overall unsolicited adverse events.

6.2.5.7 Serious Adverse Events (Pre-Crossover)

Deaths

As of September 27, 2021, 11 (<0.1%) participants in the NVX-CoV2373 arm and 5 (<0.1%) participants in the placebo arm died in the pre-crossover period. One death in the placebo arm (myocardial infarction) was assessed by the investigator as related to trial vaccine, and no deaths in the NVX-CoV2373 arm were assessed by the Sponsor as related to trial vaccine.

Deaths in the NVX-CoV2373 arm included cardiac arrest (n=5), myocardial infarction, toxicity to various agents, accidental overdose, cerebrovascular accident (CVA), gunshot wound, and septic shock. Deaths in the placebo arm included cardiac arrest (n=3), myocardial infarction, and COVID-19 pneumonia.

Of the 11 deaths in the NVX-CoV2373 arm, 4 had a clear alternative etiology, including toxicity to various agents (cocaine, fentanyl, and heroin intoxication), accidental overdose (alcohol and prescription drugs), gunshot wound to the head, and septic shock (pneumonia and blood cultures positive for *Streptococcus pneumoniae*). Details of the remaining 7 deaths are as follows:

- A 75-year-old female with a history of hypertension experienced a fatal CVA 48 days following the second dose of NVX-CoV2373. Imaging showed middle cerebral artery and intracranial internal carotid artery occlusion with large infarct. Chest X-ray showed bibasilar pneumonia with pulmonary edema. Following thrombectomy, repeat imaging revealed hemorrhagic conversion of ischemic CVA. Despite a right decompressive craniotomy, the events were fatal. Although no clear alternative etiology is identified for this CVA, this participant had several risk factors for CVA, including her age and a history of hypertension. Additionally, the concomitant pneumonia could be a contributing factor to an increased risk of stroke. The temporal distance from the most recent vaccination (>45 days) make a causative association with NVX-CoV2373 unlikely and the Sponsor and investigator's assessment that the CVA is not related is reasonable.
- A total of 5 cardiac arrests were reported (0.03% of participants). The time to onset for each event was between 12 and 58 days following the most recent NVX-CoV2373 dose. Fatal adverse events of cardiac arrest were reported 12 and 21 days after the first NVX-CoV2373 dose in a 44-year-old female and a 66-year-old male, respectively, both of whom were found pulseless and unable to be resuscitated. The 3 remaining fatal events of cardiac arrest occurred 23-, 40-, and 58-days post-Dose 2, respectively, in participants 39-, 50-, and 45-years of age, respectively. No autopsy data were available for any of these participants. Of the 5 participants with fatal cardiac arrest, 4 had co-morbidities as well as histories of substance use, including cocaine, methamphetamine, and alcohol, and 1 death was attributed to a suspected drug overdose. There was no medical history available for the remaining participant. Most participants with fatal cardiac arrests had underlying conditions that are risk factors for cardiac arrest; however, there is limited information available to assess the cause of death as autopsy data were not available. 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. While some of the fatal

events occurred within several weeks of vaccination, there were 3 similar events of cardiac arrest on Day 6, 8, and 14 post-Dose 1 in the placebo arm (0.03%), which suggests that the cases in the NVX-CoV2373 arm may reflect background rates of cardiac arrests in the study population, unrelated to vaccination. Please see Section 6.2.5.4 for additional discussion of cardiac events.

- A 79-year-old female with a history of hypertension, hyperlipidemia, sleep apnea, and morbid obesity (BMI=43.4 kg/m^2) experienced a fatal myocardial infarction 64 days following the second dose of NVX-CoV2373. This participant's age and co-morbidities are significant risk factors for myocardial infarction. In the context of these risk factors and temporal distance from vaccination (>2 months), the Sponsor and investigator's assessment that the event is not related is reasonable.

In summary, there are no deaths that appear to be clearly causally related to vaccine; fatal events were generally balanced across the treatment arms with respect to time to onset and number of cardiac-related events. However, the lack of autopsy information for multiple fatal events of cardiac arrest following NVX-CoV2373 limits assessments of causality. Please see Section 6.2.5.4 for additional discussion of cardiac events.

Serious Adverse Events

In the pre-crossover period through September 27, 2021, SAEs were reported by 199/19,735 participants (1.0%) in the NVX-CoV2373 arm and 108/9,847 participants in the placebo arm (1.1%). Related SAEs were reported by 5 participants in the NVX-CoV2373 arm (<0.1%) and 3 participants in the placebo arm. In individuals 18 to <65 years of age, SAEs were reported by 150/17,255 (0.9%) participants in the NVX-CoV2373 arm and 85/8,612 (1.0%) participants in the placebo arm. In individuals ≥65 years of age, SAEs were reported by 50/2,480 (2.0%) participants in the NVX-CoV2373 arm and 23/1,235 (1.9%) participants in the placebo arm.

In the pre-crossover period through September 27, 2021, the relative difference in the proportions of participants in each treatment arm with specific serious PTs was small (maximum relative difference per hundred= 0.03). SAEs reported by 4 or more participants in the NVX-CoV2373 arm included atrial fibrillation and acute kidney injury (n=8 [<0.1%]); cerebrovascular accident (n=7 [<0.1%]); cholecystitis acute, appendicitis (n=6 each [<0.1%]); COVID-19, cardiac arrest, prostate cancer, myocardial infarction (n=5 [<0.1%] each); pneumonia, pulmonary embolism, pneumonia aspiration, and depression (n=4 each [<0.1%]). One event each of myocardial infarction, CVA, and acute kidney injury were recorded with onset dates subsequent to withdrawal of the participant from the study; however, these are included here for the purposes of completeness.

The most common SAEs occurring at higher rates in the NVX-CoV2373 arm than the placebo arm were CVA and cholecystitis acute (7 cases in the NVX-CoV2373 arm [0.04%] vs. 0 cases in placebo arm); and atrial fibrillation (8 cases in the NVX-CoV2373 arm [0.04%] vs. 2 cases in placebo arm [0.02%]); and pneumonia aspiration and spontaneous abortion (4 cases in the NVX-CoV2373 arm [0.02%] vs. 0 cases in placebo arm). The small numbers of cases of spontaneous abortion and pneumonia aspiration do not suggest a causal relationship. Please see Section 6.2.5.4 for additional discussion of imbalances in cardiac, neurovascular, and biliary events. The most common SAEs occurring at higher rates in the placebo arm than the NVX-CoV2373 arm included COVID-19 pneumonia (1% and 0.1%, respectively), COVID-19 (0.03% and 0.06%, respectively), and suicidal ideation (0.04% and 0.01%, respectively).

A total of 5 participants in the NVX-CoV2373 arm (0.03%) and 3 participants in the placebo arm (0.03%) experienced SAEs that were considered related by the investigator. Of the SAEs in the NVX-CoV2373 arm, three were considered not related by the Sponsor, including events of headache, Basedow's disease, and thrombocytopenia. Related SAEs are summarized in Table 24.

Table 24. Serious Adverse Events Considered Related by Investigator in the Pre-Crossover Period, Safety Analysis Set, Study 301

Investigational Product	Serious Adverse Event	Onset (Days After Vaccination)[1]	Demographics/Risk Factors	Resolution	Related (Per Novavax)
NVX-CoV2373	Headache	Day 45 (PD2)	53/F History of migraines	Recovered/ Resolved	No
NVX-CoV2373	Angioedema	Day 5 (PD1)	32/F History of penicillin allergy. Urticarial eruption which progressed the following day to diffuse rash with swelling of lower lips, tongue, and periorbital area. Resolved following treatment with epinephrine, dexamethasone, diphenhydramine, and famotidine. Concurrent urinary tract infection, concomitant medication Macrobid	Recovered/ Resolved	Yes
NVX-CoV2373	Basedow's disease	Day 29 (PD2)	39/F Baseline serum, prior to vaccination, positive for elevated thyroid stimulating immunoglobin	Not recovered/ Not resolved	No
NVX-CoV2373	Thrombocytopenia	Day 32 (PD2)	63/M Hypertension, concomitant use of losartan. Laboratory testing positive for Losartan immunoglobin G platelet antibody	Recovering/ Resolving	No
NVX-CoV2373	Nervous system disorder	Day 2 (PD2)	55/M Unilateral distal left lower extremity (LLE) peripheral neuropathy, acute left peroneal nerve palsy, and acute left foot drop. Recent physical assault and alcohol intoxication.	Recovering/ Resolving	Yes
Placebo	Myocarditis	Day 73 (PD2)	31/F High cholesterol, hypertriglyceridemia, hyperlipidemia, obesity	Recovered/ Resolved	No
Placebo	Pneumonia Septic shock Acute kidney injury	Day 4 (PD2)	58/M Type 2 diabetes mellitus, hypercholesterolemia, hypertension, hyperlipidemia, neuropathy, obesity	Recovered/ Resolved	No
Placebo	Myocardial infarction	Day 7 (PD2)	70/M Type 2 diabetes mellitus, hypertension, obesity, high cholesterol, obstructive sleep apnea	Fatal	No

Source: EUA 28237 Amendment 24, Table 42.
Abbreviations: F=female; M=male; PD1=post-Dose 1; PD2=post-Dose 2
1. Day of onset post last vaccination (most recent vaccination number).

Following review of the narratives, FDA's opinion is that the event of angioedema is considered potentially related to NVX-CoV2373. The event of unilateral localized peroneal nerve injury is unlikely to be related based on plausible alternative etiology (trauma) and an implausible biological mechanism. The event of thrombocytopenia is unlikely to be related based on a plausible alternative etiology (losartan-induced). Due to plausible alternative etiologies, including laboratory data that was not available to the investigator at the time of the initial causality assessment, the vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related.

The proportions of participants with SAEs occurring within 7 or 28 days of the last dose was comparable between the NVX-CoV2373 arm (0.1% and 0.5%, respectively) and the placebo arm (0.1% and 0.5%, respectively). A total of 24 participants reported 34 SAEs within 7 days of NVX-CoV2373, including 23 events with likely alternative etiologies: appendicitis; breast cancer; prostate cancer; intervertebral disc protrusion; non-Hodgkin's lymphoma; intestinal obstruction; exacerbation of chronic kidney disease (acute kidney injury); nephrolithiasis; osteomyelitis; lower limb fracture; depression; alcohol poisoning with hypotension, pneumonia aspiration, and altered state of consciousness; COVID-19 with respiratory failure; snake bite with cellulitis and abscess; acute exacerbation of chronic congestive heart failure with onset of symptoms prior to Dose 2; cholecystitis acute associated with gallstones and histopathology consistent with chronic cholecystitis and cholelithiasis; and palpitations. One event of hypotension was reported with insufficient information to assess the case. Two events were considered related by the Sponsor (angioedema and nervous system disorder and are discussed in Table 24). The remaining 8 events in 5 participants did not have a clear alternative etiology and are described further as follows:

- A 56-year-old female participant with a history of obesity, coronary artery disease, hypertension, and hyperlipidemia reported symptoms of chest pain 2 days post-Dose 2 of NVX-CoV2373. She was diagnosed with Non-ST Elevated Myocardial Infarction (NSTEMI). Relevant laboratory test results included platelet count of 274 (units and reference range not provided) and troponin levels of 4.570 and 5.770 (reference range: 0-0.4 ng/mL). A cardiac catheterization was performed and drug-eluting stents to the circumflex and large obtuse marginal artery were placed.
- A 58-year-old male participant with a history of obesity (BMI 41 kg/m^2), high cholesterol, diabetes, and hypertension experienced an anterolateral ST elevation myocardial infarction approximately 45 minutes post-Dose 2 of NVX-CoV2373. Troponin I was normal with a result of less than 0.015 ng/mL (reference range: 0-0.045). The participant underwent a successful balloon angioplasty of the first diagonal branch, with stent placement.
- An 83-year-old male participant with a history of myocardial infarction, chronic bilateral lower extremity deep vein thromboses (DVT) with inferior vena cava filter placement, hypertension, Type 2 diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, Alzheimer's disease, and dyslipidemia presented with respiratory distress and peripheral edema 2 days post-Dose 1 of NVX-CoV2373. The platelet count was 134 K/mm^3. Computed tomography angiography (CTA) of the chest with contrast showed right lower lobar and segmental pulmonary emboli, duplex ultrasound of the bilateral lower extremities showed bilateral DVTs, and echocardiogram revealed an ejection fraction of 35-45% and severely dilated left atrium. Acute on chronic decompensated systolic congestive heart failure exacerbation, acute respiratory failure, and pulmonary embolism were diagnosed. Anti-coagulation was initiated, and the participant was discharged home. He subsequently experienced recurrent exacerbations of congestive heart failure.

- A 54-year-old male participant with a history of obesity, primary thrombophilia, recurrent deep vein thrombosis (DVT) left leg and recurrent pulmonary embolism from 2012, non-compliance issues and morbid obesity since 2012, left femoral stent placement in 2012, and stents on proximal left lower extremities presented with leg and hip pain 4 days post-Dose 1 of NVX-CoV2373 and was diagnosed with an acute DVT and pulmonary embolism.
- A 44-year-old male participant with a history of obesity, hypertriglyceridemia, proximal right coronary artery (RCA) stenosis with stent placement presented with palpitations (heart rate increased to 140 beats per minute) and chest and left arm pain on the day of the first dose of NVX-CoV2373 (following a caffeinated beverage and exercise). Electrocardiogram (EKG) was consistent with sinus tachycardia with a rate of 130 without sinus ischemic changes, and echocardiogram was normal, and the troponin was abnormal at 25 ng/L (normal: <20). The tachycardia and elevated troponin resolved overnight.

The 5 participants with cardiac events and thromboembolic events within 7 days of NVX-CoV2373 all had multiple co-morbidities with significant risk factors for the reported cardiac and thrombotic and embolic events. Attribution of causality is confounded by the presence of the pre-existing conditions and risk factors, and similar cardiac events were also reported in the placebo arm within 7 days of vaccination, including fatal events. Please see Section 6.2.5.4 for additional discussion of thrombotic and embolic events.

A total of 13 participants reported 17 SAEs within 7 days of placebo, including fatal events of myocardial infarction (considered related by the Investigator) and cardiac arrest. One participant reported events of acute kidney injury, pneumonia, and septic shock. Additional events included appendicitis (n=3), fracture (n=3), road traffic accident, panic attack, COVID-19 pneumonia, and lumbar vertebral fracture.

Please see Section 6.2.5.4 for a discussion of SAEs of particular clinical interest.

6.2.5.8 Serious Adverse Events (Post-Crossover)

Although participants originally randomized to the NVX-CoV2373 arm crossed over to receive placebo and comparisons across crossover treatment arms may discern imbalances in adverse events manifesting shortly after vaccination, prior vaccination with NVX-CoV2373 must be considered in assessments of causality for events occurring in the post-crossover period.

Deaths

As of September 27, 2021, a total of 6 (<0.1%) participants who crossed over to receive NVX-CoV2373 and 10 (<0.1%) participants who crossed over to receive placebo died in the post-crossover period. None of the deaths were considered related.

Of the 6 deaths in participants who crossed over to receive NVX-CoV2373, 4 had a clear alternative etiology (motor vehicle accident [n=2], toxicity due to various agents [toxic effects of fentanyl], and septic shock with recent diagnosis of esophageal cancer six weeks after last dose). Details of the remaining 2 deaths are as follows:

- A 35-year-old female with hypertension, obesity, and a history of alcohol and tobacco use experienced a traumatic rupture of a left vertebral artery aneurysm with subarachnoid hemorrhage, brain stem herniation, and subsequent brain death two days after the second dose of NVX-CoV2373. An autopsy was performed (reports not available), and a formal

death certificate was provided. The immediate cause of death was cerebral anoxia, as a consequence of a rupture of a left vertebral artery aneurysm. Traumatic events are a plausible alternative etiology for the aneurysmal rupture, although details on a specific trauma were not provided in the case narrative. FDA's opinion is that this event is unlikely to be related to vaccine.

- A 47-year-old male with obesity and concomitant use of quetiapine and Adderall 7 days after the second dose of NVX-CoV2373 experienced a medical emergency while out on a walk and was transported to an Emergency Room (ER) in cardiac arrest and died. An autopsy was not performed, and the death certificate could not be obtained. The cause of death was reported as cardiac arrest. At this time, there is insufficient information to assess for causal relationship to NVX-CoV2373. Cardiac events are discussed in detail in Section 6.2.5.4.

Of the 10 deaths in participants who crossed over to receive placebo, 6 had a clear alternative etiology including completed suicide, respiratory failure and chronic obstructive pulmonary disease, end stage chronic obstructive pulmonary disease, toxicity to various agents (alprazolam, oxycodone, and oxymorphone), hepatorenal syndrome (alcoholic liver cirrhosis), and alcoholic cardiomyopathy. The remaining 4 events included ischemic stroke 155 days after the Dose 2 (NVX-CoV2373) and 38 days after Dose 4 (placebo), myocardial infarction 193 days after Dose 2 (NVX-CoV2373) and 108 days after Dose 4 (placebo), and 2 events of death of unknown cause at 114 and 208 days after Dose 2 (NVX-CoV2373) and 17 and 117 days after Dose 4 (placebo), respectively. The time to onset of all events relative to the second dose of NVX-CoV2373 ranged from 83 to 224 days, making a causal relationship to NVX-CoV2373 unlikely.

Serious Adverse Events

As of September 27, 2021, SAEs were reported by 88/6,416 (1.4%) participants who crossed over to receive NVX-CoV2373 and 178/15,298 (1.2%) participants who crossed over to receive placebo. The relative difference in the proportions of participants across treatment arms in the post-crossover period with specific serious preferred terms was small (maximum relative difference per hundred=0.07). SAEs reported by 4 or more participants who crossed over to receive NVX-CoV2373 included acute myocardial infarction and COVID-19 pneumonia (n= 5 each [0.08%]), and COVID-19 and pneumonia (n= 4 each [0.06%]). The most common SAEs reported by a higher proportion of participants in the arm that crossed over to NVX-CoV2373 compared to the arm that crossed over to placebo included acute myocardial infarction (0.08% after NVX-CoV2373 and 0.01% after placebo), cholecystitis/cholecystitis chronic/cholecystitis acute (0.1% after NVX-CoV2373 and 0.02% after placebo), pneumonia (0.06% after NVX-CoV2373 and 0.02% after placebo), and coronary artery disease (0.05% after NVX-CoV2373 and 0.01% after placebo). Imbalances in cardiac and biliary events are discussed in detail in Section 6.2.5.4.

A total of 2 SAEs in the arm that crossed over to NVX-CoV2373 (<0.1%) and 3 SAEs in the arm that crossed over to placebo (<0.1%) were considered related by the investigator. None were considered related by the Sponsor. SAEs in the arm that crossed over to NVX-CoV2373 and considered related to vaccination by the investigator included an event of pulmonary embolism 7 days after the second dose of NVX-CoV2373 in a 39-year old woman with obesity, concomitant estradiol use and recent inactivity due to fatigue post-vaccination, and events of biliary dyskinesia and mild chronic cholecystitis 25 days after the second dose of NVX-CoV2373 in a 25-year old male with pathologic changes suggestive of a chronic condition. The participant

with pulmonary embolism had risk factors for clotting events, and the pathologic changes suggestive of chronicity make a causal relationship of the events of biliary dyskinesia and cholecystitis unlikely. Please see Section 6.2.5.4 for an aggregate review of cholecystitis and thrombotic/embolic events following vaccination.

SAEs in the arm that crossed over to placebo and considered related to vaccination by the investigator included lymphoma, CVA, and acute pancreatitis. The event of acute pancreatitis occurred 129 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period, which is inconsistent with a causal relationship to an acute event. The participant with lymphoma reported inguinal swelling that was present prior to randomization and enlarged after administration of NVX-CoV2373; subsequent to placebo dosing in the post-crossover period, the mass was biopsied, and the diagnosis of lymphoma was made 119 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period. The pre-existing mass prior to vaccination makes a causal relationship unlikely. The event of CVA was reported by a generally healthy 57-year-old male 73 days post-Dose 2 of NVX-CoV2373 in the pre-crossover period. Magnetic resonance imaging (MRI) showed an acute dissection of the right vertebral artery. This event was temporally distant from the last vaccination (~10 weeks). Please see Section 6.2.5.4 for an aggregate review of neurovascular events following vaccination.

SAEs within 7 days of a post-crossover dose were reported by 7 participants who crossed over to receive NVX-CoV2373 and by 12 participants who crossed over to receive placebo. The 9 SAEs reported by 7 participants within 7 days of the post-crossover NVX-CoV2373 dose included a fatal case of traumatic rupture of left vertebral artery aneurysm is described in the Deaths section above and the related case of pulmonary embolism 7 days after NVX-CoV2373 described above. The remaining events all had a clear alternative etiology (pneumonia, bacteremia, pyelonephritis, urinary tract infection, intentional self-injury, and rib fracture with pneumothorax). SAEs within 7 days of the post-crossover placebo dose included expected events in the study population, including breast lesions, uterine leiomyoma, acute cholecystitis, infectious (appendicitis, cellulitis, epididymitis), rhabdomyolysis, alcohol withdrawal syndrome, acute respiratory distress, pancreatitis, and renal cell carcinoma.

SAEs of particular clinical interest that occurred in the post-crossover period are included in the discussion in Section 6.2.5.4.

6.2.5.9 Serious Adverse Events Reported From Later Follow-Up

At FDA's request, the Sponsor provided additional safety data through a February 17, 2022, extraction date to conduct a cumulative safety evaluation through a more recent time point; however, this data is subject to further cleaning and may change.

For the pre-crossover period, a total of 12 additional SAEs were reported by 10 participants in the NVX-CoV2373 arm between September 27, 2021, and February 17, 2022, none of which were fatal or considered related, and all of which occurred >250 days after the most recent vaccination. These events included drug hypersensitivity (dilaudid), hepatic hemorrhage (due to biopsy), atrioventricular block complete, cardiac failure congestive, heart rate irregular, pancreatic neuroendocrine tumor, splenic infarction, appendicitis perforated, subdural hematoma, respiratory distress, suicidal ideation, and cerebrovascular accident. There was no specific pattern of events to reflect a long-term safety risk due to vaccine. A total of 8 additional SAEs were reported by 5 participants in the placebo arm, including one additional fatal event, all of which occurred >230 days after the most recent placebo dose. These events included

accidental overdose (insulin), gastric ulcer and gastric ulcer hemorrhage in the same participant, death (unknown cause), cerebrovascular accident, and pregnancy complications in one participant, including placenta previa, premature rupture of membranes, and premature delivery.

For the post-crossover period, SAEs were reported by an additional 62 participants who crossed over to receive NVX-CoV-2373 and an additional 127 participants who crossed over to receive placebo. The proportion of participants reporting SAEs was comparable for participants who crossed over to receive NVX-CoV2373 (2.3%) and participants who crossed over to receive placebo (2.0%). A review of SAEs including these additional events did not reveal any imbalances that were not identified in review of the data through September 27, 2021. Of the additional SAEs, 2 were considered related, including an event of COVID-19 in a participant who crossed over to receive placebo and an event of scleroderma in a participant who crossed over to receive NVX-CoV2373 (discussed in Section 6.2.5.4).

An additional 4 deaths were reported in the participants who crossed over to receive NVX-CoV2373 and an additional 13 deaths were reported in participants who crossed over to receive placebo; none of these deaths were considered related. All deaths had a time to onset of 140 days or more following Dose 4 in the crossover period. The causes of death included death (n=5); road traffic accident, multiple organ dysfunction syndrome, and septic shock (n=2 each); cardiac arrest, chronic obstructive pulmonary disease exacerbation, cardiac failure congestive, dyspnea, urosepsis, angiosarcoma, and accidental overdose (n=1 each).

Cumulatively, 26,151 participants received NVX-CoV2373 in either the pre-or post-crossover period. A total of 30 participants (0.1%) reported 41 SAEs within 7 days of NVX-CoV2373 doses. Events reported more than once included pulmonary embolism (n= 3) and hypotension (n= 2). The most commonly reported SAEs at any time following NVX-CoV2373 (at least 0.1% of participants) included COVID-19, COVID-19 pneumonia, pneumonia, atrial fibrillation, pulmonary embolism, acute kidney injury, appendicitis, and cellulitis, each of which was reported by 0.1% of vaccinated participants. In general, the cumulative reported SAEs appear consistent with expected diseases in the study population and those collected through the September 27, 2021, data cutoff.

6.2.5.10 Subgroup Analyses of Safety

Overall, the proportion of participants reporting different categories of AEs (solicited, unsolicited and SAEs) were comparable between subgroups by race and ethnicity. However, when comparing risk differences between the NVX-CoV2373 and placebo arms across the race groups, participants who are Asian and Hawaiian Pacific Islander had numerically higher reporting rates of solicited AEs, unsolicited AEs and SAEs, although these did not reach statistical significance. No significant differences in time to resolution or outcomes were observed among racial or ethnic subgroups. A detailed review of types of SAEs in these subgroups did not reveal any pattern in type of events or clear temporal association, and most were likely unrelated to vaccination. Overall AE rates were low, and therefore it is not possible to conclude based on small numbers of events whether a true difference exists. However, a potentially higher risk of adverse reactions among Asian and Pacific Island subjects cannot definitively be ruled out.

Solicited local and systemic events were reported at higher rates after the second dose of NVX-CoV2373 than after the first dose of NVX-CoV2373 among participants 18-64 years of age and ≥65 years of age. As compared with participants ≥65 years of age, participants 18-64 years of

age had higher rates of local and systemic events, with a slightly higher proportion of Grade 3 events in this younger age group. There were fewer subjects with solicited events that lasted more than 7 days in those ≥65 years of age as compared with those 18-64 years of age. Unsolicited events and SAEs rates were higher among those ≥65 years of age; the difference was driven mainly by events in the SOCs of Cardiac disorders and Vascular disorders. The risk differences between vaccine and placebo arms for these SOCs in the older cohort were similar to those in the younger cohort.

There were no notable differences in the distribution and severity of adverse events by sex.

Otherwise, there were no specific safety concerns identified in subgroup analyses by race, sex, and ethnicity, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

6.2.5.11 Pregnancy Outcomes

A summary table of pregnancy outcomes was provided by the Sponsor in their VRBPAC briefing document; however, source data was not provided, and FDA is unable to verify this data. According to the Sponsor, as of 15 March 2022, a total of 147 pregnancies were reported across the entire period of the clinical studies in participants who received NVX-CoV2373.

Table 25. Sponsor Summary of Pregnancies During Pre-Crossover Period and Post-Crossover Period Combined Number of Pregnancies With Outcomes in Participants Who Received Active Vaccine in All Clinical Studies

Pregnancy Outcome	Total NVX-CoV2373 N=147	Vaccination Before LMP N=105	Vaccination 0-30 Days After LMP N=22	Vaccination >30 Days After LMP N=9	Vaccination Relative to LMP Unknown N=11
Known pregnancy outcome, n	136	99	19	8	10
Ongoing	56	51	1	3	1
Live birth	41	24	12	3	2
Miscarriage	25	18	4	1	2
Voluntary termination	13	6	2	1	4
Ectopic pregnancy	1	0	0	0	1
Stillbirth	0	0	0	0	0
Unknown, n	11	6	3	1	1

Source: EUA 28237 Sponsor's Briefing Document in Amendment 37, Table 18
Abbreviations: LMP=last menstrual period; N=number of participants in cohort; n=number of participants with indicated outcome
Note: Data current as of 15 March 2022.

For each time period of vaccine exposure relative to the last menstrual period, the rate of miscarriage appears consistent with expected background rates in the general population; however, information on the timing of pregnancy loss and risk factors was not provided by the Sponsor. The available data are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy.

6.2.6 Summary of Study 2019nCoV-301

VE against central laboratory-confirmed mild, moderate, or severe COVID-19 over a median follow-up period of 2.5 months after completion of the primary series was 90.4% (95% CI 82.9, 94.6) for the prevention of PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination. Due to limited numbers of COVID-19 cases in the elderly, effectiveness in the elderly population was further supported by post-hoc analyses

showing similar neutralizing antibody titers in participants ≥65 years of age compared to those 50-64 years of age, for whom similar VE was observed compared to the subgroup of participants 18-64 years of age.

The available safety database (N=29,582; 19,735 originally randomized to NVX-CoV2373, 9,847 originally randomized to placebo) meets the expectations in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The EUA request was based on data through the September 27, 2021, data cutoff, which serves as the primary basis of this EUA review and conclusions. At this data cutoff point, a large majority of subjects had completed 2 months of follow-up after their series of vaccinations both pre- and post-crossover. FDA has independently verified the complete efficacy and safety data with the September 27, 2021, cutoff and analyzed additional data on deaths, PIMMCs, and SAEs through February 17, 2022. The totality of the data package submitted to the EUA meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events were more common after NVX-CoV2373 compared to placebo, with increased frequency and severity following the second dose. The most frequently reported local AR was injection site pain/tenderness. After NVX-CoV2373, any Grade 3 local AR was reported by 1.1% of participants post-Dose 1 and 6.6% of participants post-Dose 2. Grade 4 local ARs were only reported following the second dose of NVX-CoV2373 and occurred in <0.1% of participants. The median time to onset for any local AR was 2 days following vaccination and the median duration was 2-3 days. After NVX-CoV2373, Grade 3 and 4 solicited systemic ARs were reported by <1.5% and <0.1% of participants, respectively, post-Dose 1 and by 12% and 0.1% of participants, respectively, post-Dose 2. In both treatment groups and for both Dose 1 and 2, fatigue/malaise, headache, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs. For any solicited systemic AR, the median time to onset was 2 days and the median duration was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms.

Multiple events of myocarditis/pericarditis were reported in temporal relationship to NVX-CoV2373 across pre-market clinical studies, and FDA considers some of these events potentially related to vaccination. Events of lymphadenopathy were infrequent but reported by a higher proportion of participants in the NVX-CoV2373 arm, with the highest rate observed after Dose 2 (0.2%). Hypersensitivity reactions were infrequent at 0.1% of NVX-CoV2373 recipients but in reported at a higher proportion than placebo (0.03%). Additionally, serious event of angioedema, although causality to vaccine may be confounded, was reported. Review of the data also identified several numerical imbalances in specific adverse events of particular interest, although a conclusion of causal association cannot be made based on available data; these include thromboembolic events, including cardiac and neurovascular events, cholecystitis, uveitis, cardiac failure, and cardiomyopathy.

7. Additional Safety Data

Additional safety data (SAEs and AESIs, including PIMMCs) were reviewed from 3 studies: Study 101, 501- and 302; NVX-CoV2373 vaccine manufactured at Emergent BioSolutions was administered as the primary series. For Study 101 (parts 1 and 2), safety data from only those participants who received the 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant vaccine formulation are presented in this section. See Appendix B for study description and population demographic and baseline characteristics.

SAEs, AESIs, and PIMMCs were monitored throughout the studies, starting from Dose 1, and safety data collection is ongoing. FDA reviewed analyses derived from data available through the following dates:

Table 26. Duration of Safety Follow-up, Safety Analysis Set

Study	NVX-CoV2373 N	Placebo N	Total % of Participants Completing at Least 2 Months of Safety Follow-up After Dose 2	Date of Crossover, Unblinding, End of Study[a], Booster[b] or Data Cutoff[c]
302	7569	7570	81.2%	February 23, 2021
501	2211	2197	95.4%	February 23, 2021
101, Part 1	29	23	0%	December 19, 2020
101, Part 2	514	255	97.6%	December 15, 2020

Source: FDA-generated table.
N: number of participants who received at least 1 dose of study product.
a. Study 2019nCoV-101, Part 1.
b. Study 2019nCoV-101, Part 2.
c. The date reflects whichever timepoint came first.

The median duration of follow-up after Dose 2 was 2.7 months (study 302), 3 months (study 501), 6.3 months (study 101, part 2) and 1.2 months (study 101, part 1).

Events of clinical interest in Study 302 included:

- One event of myocarditis was reported by a 19-year-old male in the NVX-CoV2373 arm who developed myocarditis 2 days after Dose 2. Details of this event are provided in Table 21.
- One event of Guillain-Barre syndrome was reported by a 65-year-old female NVX-CoV2373 recipient who experienced progressive neuropathy starting 9 days following Dose 1. Some of her neuropathy symptoms were consistent with features of Guillain-Barre syndrome. Initially, she experienced hand paresthesias, which gradually progressed to numbness of feet during the month, and eventually required a walker for walking. The participant received the second dose of vaccine 21 days after the first dose of vaccine as scheduled. After approximately 4 months, she developed pain in the shoulder, back, and hip. The subject was treated with tramadol and pregabalin. The study investigator and consulting neurologist also considered the progressive neuropathy to be related to vaccination. FDA agrees with the study investigator's assessment.

There were no new SAEs, AESIs or PIMMCs in studies 101, 302, or 501 that were considered at least possibly related by FDA that were not previously identified in study 301.

8. Foreign Postmarketing Experience

This section describes postmarketing reports (for data available prior to the June 7 VRBPAC meeting) of adverse events following administration of Novavax COVID-19 Vaccine in other countries. Data from passive surveillance systems are subject to several limitations, including but not limited to 1) potential reporting bias (underreporting or stimulated reporting), 2) possible missing or inaccurate information in reports, 3) lack of a control group, 4) reported diagnoses are not necessarily medically confirmed diagnoses, and 5) reporting behaviors may vary between countries. Due to these limitations, passive surveillance data alone are generally insufficient for determining causality for a given adverse event after vaccination. Nonetheless, postmarketing reports can serve as a useful tool for detecting unusual or unexpected patterns of

adverse events (also known as "safety signals") that warrant further investigation or corroboration with other data sources (Shimabukuro et al, 2015; UMC, 2021).

The Sponsor submitted their third Monthly Safety Summary Report (MSSR), covering reporting period April 1, 2022, to April 30, 2022, for review during this EUA request. MSSRs contain worldwide interval and cumulative postmarketing safety data for NVX-CoV2373 (including vaccine distributed to foreign markets under the trade names Nuvaxovid and Covovax). Cumulatively, more than 41 million doses of NVX-CoV2373 were distributed globally. Among countries/jurisdictions with available administration data (i.e., Australia, Canada, European Union, New Zealand, and South Korea), 744,235 NVX-CoV2373 doses had been administered cumulatively. The Sponsor's global vaccine safety database for NVX-CoV2373 contained a cumulative total of 923 spontaneous Individual Case Safety Reports (ICSRs), representing a total of 3,859 adverse events (AEs). Of these AEs, 424 were serious and unlisted, 124 were serious and listed, 2,012 were non-serious and unlisted, and 1,299 were non-serious and listed. There was one pregnancy-related ICSR and no fatal ICSRs reported.

The Sponsor identified myocarditis and pericarditis as a new "potential safety signal" in their third MSSR. As of April 30, 2022, a total of 37 individual case safety reports (ICSRs) for myocarditis and pericarditis were received, involving a total of 38 adverse events (AEs). Two of these ICSRs were identified as duplicates and invalidated, leaving a total of 35 valid cumulative ICSRs representing 36 AEs. Of these 35 valid ICSRs, 14 were considered medically confirmed and 21 were non-medically confirmed. The Sponsor performed observed-to-expected (O/E) analyses for both the cumulative AEs (n=38) and AEs from medically confirmed cases only (n=14). The Sponsor used a background rate from ACCESS (vACCine covid-19 monitoring readinESS project), an open access resource of 10 data sources from seven European countries (VAC4EU, 2019; EMA, 2020). O/E analyses for the cumulative AEs revealed significantly elevated O/E rate ratios for both the main analysis (RR 4.95, 95% CI 3.50 - 6.79) as well as sensitivity analyses that assume a reporting sensitivity of 50% (RR 9.90, 95% CI 7.00 – 13.58) and 25% (RR 19.79, 95% CI 14.01 – 27.17), respectively. O/E rate ratios for the medically confirmed cases only were also elevated (RR 1.82, 95% CI 1.00 – 3.06), but statistically significant only for the sensitivity analyses (reporting sensitivity of 50%: RR 3.65, 95% CI 1.99 – 6.18; reporting sensitivity of 25%: RR 7.29, 95% CI 3.98 – 12.23). The majority of ICSRs for myocarditis and pericarditis were submitted from Australia's Therapeutic Goods Administration (TGA). The Sponsor planned to review additional report details from the TGA and adjudicate a subset of reports against a case definition.

FDA reviewer assessment of the limited report details provided in the third MSSR for the 35 valid cases showed that the 36 associated AEs were coded with the following Preferred Terms (PTs): Pericarditis (n=29), Myocarditis (n=4), Myopericarditis (n=2), and Carditis (n=1). The median known age was 34 years (range 23 – 62 years) and there were more males (n=20) than females (n=15). Outcomes were reported as follows: Unknown (n=14), Not Recovered/Not Resolved (n=17), Recovering/Resolving (n=2), Recovered with Sequalae (n=1), and Recovered/Resolved (n=1). In addition, six reports involved recurrent pericarditis. In five of these cases, the prior episode of pericarditis was reported to have occurred following an mRNA COVID-19 vaccine.

The FDA queried the World Health Organization's VigiBase on May 31, 2022 (UMC, 2022a). VigiBase is a global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC), with around 150 actively contributing

countries (UMC, 2022b). The information presented here does not represent the opinion of the UMC or the World Health Organization. Reports come from a variety of sources and the probability that the suspected adverse effect is drug-related is not the same in all cases. For additional details on the limitations and conditions of VigiBase, see the UMC Caveat Document (UMC, 2021). This query revealed a total of 1,677 reports for Novavax COVID-19 Vaccine. The following three countries accounted for over 90% of reports: Australia (n=726; 43.3%), Germany (n=709; 42.3%), and Italy (n=122; 7.3%). Two hundred sixty-six (15.9%) reports were serious, and 1,411 (84.1%) reports were not serious. The ten most common adverse events (AEs) in reports (represented by MedDRA Preferred Terms [PTs]) were: 1) Headache (n=440; 26.2%), 2) Fatigue (n=341; 20.3%), 3) Chest pain (n=223; 13.3%), 4) Pyrexia (n=223; 13.3%), 5) Dizziness (n=222; 13.2%), 6) Myalgia (n=222; 13.2%), 7) Nausea (n=193;11.5%), 8) Injection site pain (n=176;10.5%), 9) Paraesthesia (n=174; 10.4%) and 10) Chills (n=149; 8.9%). Among the 1,677 reports for Novavax COVID-19 Vaccine overall, 46 reports contained 48 AEs pertinent to myocarditis/pericarditis: Pericarditis (n=37), Myocarditis (n=6), Myopericarditis (n=4), and Carditis (n=1). Most of these reports (n=41; 89.1%) were from Australia.

9. FDA Review of Other Information Submitted

9.1 Chemistry, Manufacturing, and Control (CMC) information

The Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373 vaccine) contains a recombinant full-length SARS-CoV-2 spike glycoprotein (rS) that is expressed from a recombinant baculovirus vector in *Spodoptera frugiperda* (Sf9) insect cells, purified by (b) (4) chromatography and formulated in a buffer containing sodium phosphate, sodium chloride, and polysorbate 80. The drug product (DP) is a co-formulation of the rS antigen drug substance (DS) with Matrix-M, a saponin-based adjuvant derived from the bark of *Quillaja saponaria* Molina and formed into matrix particles with phosphatidylcholine and cholesterol.

Production of the (b) (4) for clinical development has evolved from a (b) (4) scale produced at a Contract Manufacturing Organization (CMO) for Phase 1/Phase 2 trial, to a (b) (4) scale produced at a different CMO for Phase 3 study. The EUA request is also based on a (b) (4) process; however, the intended commercial product is being produced at a manufacturing facility that is different from the CMO that produced the clinical trial material (CTM) for Phase 3 study. In addition, two (b) (4) DS processes, Process-1 and Process-2, are used at the facility supporting the EUA. Both Process-1 and Process-2 have been validated with the manufacture of 3 process performance qualification (PPQ) lots. A comprehensive analytical comparability assessment has been performed and the data support quality comparability of (b) (4) DS lots from the supply site for Phase 3 and the PPQ lots from both processes at the facility supporting the EUA.

During the late stage of the EUA review, the sponsor informed FDA of manufacturing changes that were introduced to the (b) (4) DS manufacture for EUA supply. The sponsor manufactured 3 lots of (b) (4) DS with the implemented process changes; the 3 lots met release specifications and are comparable to DS lots manufactured with the currently validated manufacturing process. These minor manufacturing changes do not appear to have any apparent impact on the purity, potency, and quality of (b) (4) DS.

Matrix-M is manufactured by mixing Matrix-A and Matrix-C, each of which is produced separately as a mixture of saponin extracts and lipid solutions. During earlier clinical

development through Phase 3, Matrix-A and Matrix-C were manufactured at a small-scale in a single facility. Two more facilities are added under the EUA request to produce Matrix-A and Matrix-C. To support the EUA, in-process, release, and characterization data for a minimum of three process performance qualification batches of Matrix-A and Matrix-C manufactured from the 3 different facilities were provided. Comprehensive analytical comparability assessments have been performed and the data submitted support the comparability of Matrix-A and Matrix-C produced from all 3 facilities.

The NVX-CoV2373 drug product (DP) is manufactured by mixing the rS antigen DS with Matrix-A and Matrix-C followed by sterile filtration and fill/finish. Like the DS production, the CTM DP lots were produced at a smaller scale at a CMO that was different from the facility supporting the EUA request. The commercial scale DP process for the EUA request was validated by producing three PPQ lots. A comprehensive analytical comparability assessment has been performed and the data support quality comparability of DP lots from the supply site for Phase 3 trial and the DP PPQ lots from the production site supporting the EUA request. The sponsor will submit the Certificates of Analysis of lots to be distributed under EUA, at least 48 hours prior to distribution, for FDA review and concurrence.

Stability studies have been designed to support use of the vaccine under the EUA. All available stability data generated with NVX-CoV2373 DS and DP lots support the emergency deployment of Novavax COVID-19 Vaccine, Adjuvanted. All stability studies of the DS and DP lots are ongoing and will continue to be monitored. Data will be submitted to the IND as they become available.

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

The manufacture of Novavax COVID-19 Vaccine is performed at Serum Institute of India Pvt. Ltd (SIIPL). For this facility, the FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the March 2022 guidance, “Emergency Use Authorization for Vaccines to Prevent COVID-19”, to ensure that there is adequate control of the manufacturing processes and facilities. In addition, FDA conducted a site inspection of SIIPL from April 11 – 19, 2022 to support this EUA request. The SIIPL facility appears adequate to manufacture Novavax COVID-19 Vaccine under an EUA.

9.2 Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan (Version 0.1, dated January 20, 2022) to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine. In this initially proposed Pharmacovigilance Plan, the Sponsor identified vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease, myocarditis and pericarditis, and anaphylaxis as important potential risks. Use in pregnancy and while breast feeding, 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. After

further discussion with FDA, the Sponsor submitted a revised Pharmacovigilance Plan (Version 0.3, dated June 27, 2022) which recharacterized "anaphylaxis" and "myocarditis and/or pericarditis" as important identified risks. 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 Multisystem Inflammatory Syndrome in adults
- 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 (OBPV). 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 five planned surveillance studies.

- Pregnancy Exposure Registry: The Sponsor plans to use the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)—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.
- 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 adults 18 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 adults 18 years of age and older 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.

The Sponsor agreed to include safety outcomes in the two active safety surveillance studies for certain cardiac, neurovascular, thromboembolic, autoimmune/inflammatory, and biliary events. These safety outcomes will further evaluate adverse events observed in clinical trials.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

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 Multisystem Inflammatory Syndrome in adults
- 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.

9.3 Clinical Assay Information

Two clinical diagnostic assays (Roche Elecsys anti-SARS-CoV-2 assay and Abbott RealTime Quantitative SARS-CoV-2 Assay) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. Prior to vaccination with NVX-CoV2373 or placebo, the baseline serostatus of study enrollees in the clinical trial was determined using the Roche

Elecsys Anti-SARS-CoV-2 assay. The Elecsys anti-SARS-CoV-2 assay is an antibody-based electrochemiluminescence immunoassay used for the qualitative detection of antibodies to the nucleocapsid (N) protein of SARS-CoV-2 in clinical serum and plasma samples. The diagnosis of SARS-CoV-2 infection during clinical study was confirmed with the Abbott RealTime Quantitative SARS-CoV-2 Assay that targets the amplification of unique regions of the RNA-dependent RNA polymerase (RdRp) and the N genes. Both the Roche Elecsys and the Abbott RealTime Quantitative SARS-CoV-2 Assay were validated for performance at the University of Washington (Novavax's testing site) and are suitable for utility in SARS-CoV-2 diagnosis.

Diagnostic assays supporting other clinical trials conducted in Australia, the United Kingdom and South Africa, are also authorized for emergency use and verified for performance at the testing laboratories.

9.4 Inspections of Clinical Study Sites

Bioresearch Monitoring (BIMO) inspections were conducted at five domestic clinical investigator study sites participating in the conduct of study protocol 2019nCoV-301: *A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M1™ Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years).* FDA did not identify any major deficiencies regarding the clinical investigators' conduct of the study, and no data integrity issues were identified. Additionally, FDA's review of the study-wide compliance information from the study did not identify systemic concerns with trial conduct across the other study sites.

9.5 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. In anticipation of a future submission to support use of the Novavax COVID-19 Vaccine, Adjuvanted as a booster dose, the EUA Fact Sheets and Letter of Authorization will refer to the authorized 2-dose series as a primary series.

9.6 Non-Clinical Studies

Toxicology Studies

To support the EUA, Novavax Inc. referred the following two toxicology studies of Sars-CoV-2 rS vaccine with matrix M1 adjuvant that have been reviewed under their IND 22430:

1. 57-Day Repeat dose Intramuscular Toxicity Study of SARS-CoV-2 rS nanoparticle vaccine with and without Matrix-M1 Adjuvant in the New Zealand White Rabbit Followed by a 21-Day recovery period (study # 702-091)
2. Developmental and Reproductive Toxicology Study of SARS-CoV-2 rS with Matrix-M1 Adjuvant in Rats (study # 702-096)

In the developmental toxicity study of SARS-CoV-2 rS, three groups of 50 female rats were administered intramuscularly vehicle control article, 50 ug SARS-CoV-2 rS plus 10 ug of matrix-M1 or 10 ug Matrix-M1 in 0.1 mL 27 days and 13 days prior to mating and on gestation days 7

and 15. The animals in each group were divided into delivery and cesarean cohorts. There were no effects on mating performance, fertility, fetal weight, or any naturally delivery or little parameters. It did not produce any fetal external, visceral, or skeletal malformations and variations.

Thus, SARS-CoV-2 rS administered to female rats prior to mating and during gestation periods at dose of 5 ug in 10 ug of matrix-M1 adjuvant did not have any effects on female fertility, fetal/embryonal development and postnatal developmental effects.

Other Non-Clinical Studies

Several non-clinical studies in mice, Syrian hamsters, and non-human primates (NHPs) were conducted to support the safety and efficacy of NVX-CoV2373. The rS antigen/Matrix-M adjuvant combination induced a balanced Th1/Th2 response as determined by IgG1/IgG2a ratios in mice. The rS antigen drug substance lots used in the various non-clinical studies were manufactured at a smaller scale and mixed with the adjuvant at the time of inoculation. Animals were inoculated by the intramuscular route as proposed for clinical administration of NVX-CoV2373, and a dose range of rS antigen with or without Matrix-M were tested in different animal models. In all non-clinical studies, animals were inoculated on a prime/boost schedule at an interval of 14 days or 21 days. The results from the animal studies demonstrated that rS antigen formulated with Matrix-M consistently enhanced the levels of rS-specific IgG antibody, hACE2 binding inhibiting antibodies, and SARS-CoV-2-neutralizing antibodies. In addition, adjuvanted rS antigen induced T-cell responses including Th1-type polyfunctional $CD4^+$ T-cell expressing IFN-γ, TNF-α, and IL-2 at higher levels than Th2-type $CD4^+$ T-cells expressing IL-4 in mice. A similar induction of polyfunctional $CD4^+$ T-cells with a predominance of Th1 phenotype (IFN-γ-producing cells) was detected in baboons vaccinated with a formulation comparable to the proposed clinical dose of NVX-CoV2373. Spike-specific antibodies and IFN-γ-producing T-cells were detectable for at least 6 months in baboons.

In addition, animals vaccinated with adjuvanted rS antigen were protected from a subsequent challenge with SARS-CoV-2 (USA-WA1) as determined by clearance of virus from lungs and protection from weight loss in mice and hamsters, protection from lung pathology in hamsters, and absence of sub-genomic RNA in bronchoalveolar lavage and nasal swabs in cynomolgus macaques. No evidence of vaccine-induced enhancement of disease was found after virus challenge in mice vaccinated with sub-optimal doses of NVX-CoV2373, as well as in vaccinated Syrian hamsters, rhesus and cynomolgus macaques.

Preliminary data also indicate that immune responses induced by Matrix-M adjuvanted rS antigen provide dose-dependent protection against the B.1.617.2 (Delta) and BA.1 (Omicron) SARS-CoV-2 variants of concern in mice, as demonstrated by significantly reduced lung viral loads (Delta and Omicron) and body weight loss (Delta) as compared to placebo controls in animal challenge studies. *In vitro*, antibodies elicited in mice by vaccination with Matrix-M-adjuvanted rS antigen neutralized the B.1.1.7 (Alpha), B.1.351 (Beta), P1 (Gamma), B.1.621 (Mu), B.1.617.2 (Delta), AY1 (Delta plus) to levels comparable to the prototype SARS-CoV-2 (USA-WA1). Neutralization titers against Omicron BA.1 were lower compared to those against the other strains and variants tested.

10. Benefit/Risk Assessment in the Context of the Proposed Indication and Use Under EUA

10.1 Known and Potential Benefits

The known benefits among vaccine recipients 18 years of age and older relative to placebo are reduction in the risk of mild to severe COVID-19 occurring at least 7 days after the second primary series vaccination. Vaccine efficacy estimates from study 301 are generally consistent across subgroups stratified by demographic variables (including age, race, and ethnicity) and risk for severe COVID-19, with variability in efficacy estimates for some subgroups likely due to small numbers of cases reported in those subgroups. Although only 4 severe cases occurring at least 7 days after the second primary series vaccination were reported in the study, all 4 severe cases were in the placebo arm. This observation is consistent with the consistent observation that preventive vaccines, including other COVID-19 vaccines that have been authorized or approved for use in the US, are generally more effective at preventing severe disease than preventing mild disease.

10.2 Uncertainties in Benefits

Effectiveness against Currently Circulating SARS-CoV-2 Variants

The study enrollment and efficacy follow-up occurred during December 27, 2020, to September 27, 2021, and mainly when the Alpha variant of SARS-CoV-2 was predominant and prior to the emergence of Delta and Omicron variants. Post-authorization experience with other COVID-19 vaccines has demonstrated substantially decreased effectiveness of a primary series against the currently circulating Omicron variant and sublineages, in particular against milder COVID-19, than was demonstrated in pre-authorization clinical trials conducted when the ancestral strain was circulating. Relevant data to assess effectiveness of NVX-CoV2373 against the Omicron variant and sublineages, including observational data from use in other countries where the vaccine has been deployed, are currently unavailable; however, based on the efficacy estimate in the clinical trial of this vaccine, it is more likely than not that the vaccine will provide some meaningful level of protection against COVID-19 due to Omicron, in particular against more severe disease. The extent to which a booster dose, administered at some time after completion of the primary series, would provide additional protection remains a question to be further evaluated.

Duration of Protection

The analyses have a limited length of follow up, therefore, it is not currently possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in Certain Populations at Higher Risk of Severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) and participants with cardiovascular, chronic renal, and chronic liver disease are too small to evaluate efficacy outcomes. Additionally, few cases of PCR-confirmed COVID-19 were analyzed for participants ≥65 years of age, limiting the robustness of the efficacy estimate for this age subgroup.

Effectiveness in Individuals Previously Infected With SARS-CoV-2

There were no COVID-19 cases reported in individuals with prior SARS-CoV-2 infection. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred by natural immunity (Plumb et al, 2022). Additionally, for individuals previously infected with the Omicron variant of SARS-CoV-2, a vaccine based on the ancestral strain S protein could provide a greater breadth of protection against other SARS-CoV-2 variants.

Effectiveness in Pediatric Populations

Data to directly inform vaccine effectiveness in pediatric age groups (17 years of age and younger) were not included or considered as part of this EUA request. If the vaccine is authorized under EUA for use in adults, data from studies in pediatric age groups could be considered in EUA amendments to expand the authorized use to include those age groups.

Future Vaccine Effectiveness as Influenced by Characteristics of the Pandemic

The continued evolution of the pandemic, including changes in the virus infectivity, antigenically significant mutations to the S protein, and changes in practice of nonpharmacologic interventions to mitigate against transmission, will likely influence vaccine effectiveness over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical.

Effectiveness Against Long-Term Effects of COVID-19 Disease

Available data are not conclusive on the effectiveness of COVID-19 vaccines currently in use against long-term sequelae of COVID-19 among individuals who are infected despite vaccination. Additional evaluation is needed to assess the effect of this vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Effectiveness Against Asymptomatic Infection and Transmission

Available data for COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against symptomatic COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections. Data for these outcomes are not currently available for NVX-CoV2373, it is more likely than not that the observations with other COVID-19 vaccines (with similar antigens and routes of administration) will apply to this vaccine as well.

10.3 Known and Potential Risks

In clinical evaluation, local and systemic ARs, usually lasting 1 to 3 days, were reported at higher frequencies among NVX-CoV2373 recipients as compared to placebo recipients. The most common solicited adverse reactions were injection site pain/tenderness, malaise/fatigue, headache, and myalgia (muscle pain). Overall, solicited reactions were reported more commonly in younger participants. Hypersensitivity reactions and lymphadenopathy were observed post vaccination. Reporting rates of MAAEs, SAEs, and PIMMCs in the clinical trials were generally low and balanced between NVX-CoV2373 and placebo arms.

Myocarditis/pericarditis events were identified across the clinical development program, including four events of myocarditis and/or pericarditis (and one additional event that in FDA's assessment is clinically consistent with myocarditis) within 10 days of vaccination. There were no myocarditis/pericarditis cases in the placebo arm within 28 days post vaccination. These events raise the concern for a causal association with this vaccine, similar to the association documented with mRNA COVID-19 vaccines. Data from passive surveillance during post-authorization use in other countries also indicate a higher-than-expected rate of myocarditis and pericarditis (mainly pericarditis) associated with the vaccine. However, interpretation of these passive surveillance data is not straightforward, and further evaluation is needed to inform the risk of myocarditis and pericarditis associated with this vaccine, and their outcomes, as additional data emerge over time.

One case of Guillain-Barré syndrome was observed in the clinical development program, in temporal association post-vaccination and without an identified alternative cause. Guillain-Barré syndrome is known to be associated with other vaccines.

10.4 Uncertainties in Risks

Safety in Certain Subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children, pregnant and lactating individuals and their infants, and immunocompromised individuals.

Adverse Reactions that are Uncommon or that Require Longer Follow-Up to be Detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the clinical trial safety population.

Certain adverse events of clinical interest were reported infrequently in the clinical trials but with small numerical imbalances or differences in temporal association between the NVX-CoV2373 and placebo arms, including events of Guillain-Barré syndrome, cholecystitis, cardiac failure/cardiomyopathy, thromboembolic events, and uveitis.

Active and passive safety surveillance will continue during the post authorization period to further evaluate these events and to detect new safety signals.

11. VRBPAC Summary

The 173rd meeting of the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) was held on June 7, 2022, to consider Novavax, Inc.'s EUA request for a vaccine to prevent COVID-19 in individuals 18 years of age and older. The meeting included presentations by staff from the Centers for Disease Control and Prevention on the current epidemiology of COVID-19 and COVID-19 vaccination rates in the United States and an overview of COVID-19 vaccine associated myocarditis. Novavax, Inc. then presented data from their ongoing studies in support of their EUA request followed by FDA's independent assessment of the data and a period for questions from committee members. The meeting day included an Open Public Hearing.

In their discussions, committee members generally agreed that available clinical efficacy data supported the benefit of the Novavax COVID-19 Vaccine, Adjuvanted but noted the limitations of clinical endpoint efficacy data assessed prior to emergence of the Omicron variant. Committee members also commented on lower efficacy estimates in the Hispanic/Latino population and individuals 65 years of age and older compared to the overall study population. Committee members stressed the importance of post-authorization assessments of vaccine effectiveness in these subgroups as well as in the setting of continually evolving epidemiology of the COVID-19 pandemic. The likely need for booster doses following a primary series of Novavax COVID-19 Vaccine, Adjuvanted, was also discussed extensively.

Committee members also generally agreed that available safety data was favorable to support EUA but stressed the importance of continued post-authorization safety surveillance, in particular for myocarditis/pericarditis, and endorsed that reported events consistent with myocarditis/pericarditis in clinical trials of Novavax COVID-19 Vaccine, Adjuvanted provided reasonable evidence of a causal association, thereby supporting inclusion of a Warning statement in EUA Fact Sheets if the vaccine were to be authorized for use under EUA.

Following the presentations and committee discussion, the VRBPAC voted 21-0 (with 1 abstention) in favor of a determination that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted 2-dose series outweigh the known and potential risks for use in individuals 18 years of age and older.

12. Overall Summary and Recommendations

Following review of information submitted in support of the EUA request and considering VRBPAC recommendations from the June 7, 2022 meeting, the review team concludes that:

- As summarized in Section 2 of this review, 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 an adequate and well-controlled trial described in Section 6 of this review, the Novavax COVID-19 Vaccine, Adjuvanted, when administered as a 2-dose primary series to individuals 18 years of age and older, may be effective in preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2. In the final scheduled primary efficacy analysis, VE against PCR-confirmed mild, moderate, or severe COVID-19 was 90.4% (95% CI 83.8, 94.3). The efficacy estimate was lower in participants ≥65 years of age at 78.6% (95% CI -16.6, 96.1) and in participants of Hispanic/Latino ethnicity at 77.0% (95% CI: 48.7%, 89.7%) compared to the overall study population, although the case numbers for these subgroups were small. Efficacy outcomes were consistently robust (≥90%) across other demographic subgroups and in participants with medical comorbidities associated with higher risk of severe COVID-19.

- Based on the data summarized in Sections 6 and 7 of this review and assessment of benefits and risks in Section 10 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of

age and older. Known benefits include reduction in the risk of confirmed COVID-19 occurring at least 7 days after dose 2, and reduction in the risk of moderate and severe COVID-19. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Uncertainties related to benefits include effectiveness against currently circulating and future SARS-CoV-2 variants; effectiveness against long term effects of COVID-19 disease; and duration of protection. Known risks include common local and systemic adverse reactions and less common hypersensitivity reactions, chills, injection site pruritus, lymphadenopathy related events, and myocarditis/pericarditis. Uncertainties and potential risks that should be further evaluated include safety in certain subpopulations (including younger age groups and pregnant and breastfeeding women), whether vaccine-enhanced disease could occur with waning of immunity, and adverse reactions that are uncommon or that require longer follow-up to be detected, including imbalances observed in study 301: Guillain-Barré syndrome, biliary events, neurovascular events, cardiac events, thromboembolic events, and uveitis.

- As summarized in Section 3 of this review, mRNA-based vaccines Comirnaty and Spikevax are the only FDA-approved vaccines indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted would provide an alternative vaccine platform (recombinant protein plus adjuvant) to prevent COVID-19 caused by SARS-CoV-2 for individuals 18 years of age and older who, for example, have contraindications to the approved mRNA-based vaccines.

Based on the considerations outlined above, the review team recommends issuance of an EUA for use of the Novavax COVID-19 Vaccine, Adjuvanted for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

13. References

Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data – United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228-1232. Published 2021 Sep 3. Doi:10.15585/mmwr.mm7035e5.

Centers for Disease Control and Prevention (CDC), 2022a, COVID Data Tracker Trends in Number of COVID-19 Cases and Deaths in the US Reported to CDC, by State/Territory, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases. Accessed May 13, 2022.

CDC, 2022b, COVID Data Tracker Variant Proporitons, https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed May 13, 2022.

CDC, 2022c, COVID Data Tracker COVID-NET Laboratory-confirmed COVID-19 hospitalizations, https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed May 13, 2022.

Chen C, Haupert SR, Zimmermann L, et al. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review, *J. Infect. Dis.*, 2022;, jiac136, https://doi.org/10.1093/infdis/jiac136.

Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ. 2021;373:n1098. Published 2021 May 19. Doi:10.1136/bmj.n1098.

European Medicines Agency (EMA), 2020, EMA commissions independent research to prepare for real-world monitoring of COVID-19 vaccines 2020. Available from: https://www.ema.europa.eu/en/news/ema-commissions-independent-research-prepare-real-world-monitoring-covid-19-vaccines. Accessed May 27, 2022.

Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol 19, 75–77 (2022). https://doi.org/10.1038/s41569-021-00662-w.

Murk W, Gierada M, Fralick M, et al. Diagnosis-wide analysis of COVID-19 complications: an exposure-crossover study. CMAJ. 2021;193(1):E10-E18. Doi:10.1503/cmaj.201686

Plumb ID, Feldstein LR, Barkley E, et al. Effectiveness of COVID-19 mRNA Vaccination in Preventing COVID-19–Associated Hospitalization Among Adults with Previous SARS-CoV-2 Infection — United States, June 2021–February 2022. Morb Mortal Wkly Rep 2022;71:549-555. DOI: http://dx.doi.org/10.15585/mmwr.mm7115e2

Shimabukuro T, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398-405. Epub July 22, 2015. doi: 10.1016/j.vaccine.2015.07.035.

Uppsala Monitoring Centre (UMC), 2021, Caveat Document 2021. Available from: https://who-umc.org/media/yzpnzmdv/umc_caveat.pdf. Accessed May 26, 2022.

UMC, 2022a, PV Products: VigiLyze 2022 (updated May 13, 2022). Available from: https://who-umc.org/pv-products/vigilyze/. Accessed May 27, 2022.

UMC, 2022b, About VigiBase, 2022b. Available from: https://who-umc.org/vigibase/. Accessed May 26, 2022.

VAC4EU, 2019, Toolbox: Dashboard Background rates of Adverse Events of Special Interest for COVID-19 vaccines 2019. Available from: https://vac4eu.org/covid-19-tool/. Accessed May 27, 2022.

Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020 Aug;217:108480. doi: 10.1016/j.clim.2020.108480. Epub 2020 May 24. PMID: 32461193; PMCID: PMC7246018.

World Health Organization (WHO), 2022, WHO Coronavirus (COVID-19) Dashboard, https://covid19.who.int/. Accessed May 26, 2022.

Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-706.

14. Appendix A. Other Clinical Studies

14.1 Study 2019nCoV-302

Study 302 is an ongoing Phase 3, randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of NVX-CoV2373 in adults ≥18 years of age in the United Kingdom, and included adults at risk to develop severe COVID-19: obesity (BMI >30 kg/m^2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2, life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2).

Of the total of 15,139 adults randomized 1:1 (NVX-CoV2373: saline placebo), 7,569 NVX-CoV2373 and 7,570 placebo recipients were included in the safety analysis set. During the course of study, 34.6% (2,555 NVX-CoV2373, 2,680 placebo) were unblinded to the vaccine assignment because they became eligible and elected to receive an EUA-approved COVID-19 vaccine, and approximately 98% of the unblinded participants continued safety evaluations in the study.

Of the total study population, 27.2% of participants were 65-84 years of age; 48.4% were female; <5% were Asian or Black, 94.3% were White; 0.8% were Hispanic/Latino; 26.3% were obese; 44.7% had a medical history of at least 1 comorbid condition reported, or obesity; and 4.2% of participants had evidence of SARS-CoV-2 infection (by ELISA) at Day 0.

14.2 Study 2019nCoV-501

Study 501 is an ongoing Phase 2, randomized, observer-blind, placebo-controlled study to evaluate the efficacy, immunogenicity, and safety of NVX-CoV2373 in adults 18-84 years of age in South Africa. HIV-positive adults were eligible to enroll in the study if they were receiving highly active antiretroviral therapy, had no opportunistic infections in the 1 year prior to the first study vaccination, and had a HIV-1 viral load <1,000 copies/mL within 45 days of randomization.

Of the total 4,419 adults randomized 1:1 (NVX-CoV2373: saline placebo), 2,211 NVX-CoV2373 and 2,197 placebo recipients, including 244 HIV-positive recipients (122/per study group) were included in the safety analysis set.

The demographic and baseline characteristics of the study population are as follows:

- HIV-negative population (n=4,164): 4.4% were 65-84 years of age; 95% were Black, 41% were female; 1.5% were Hispanic/ Latino; 77.8% had no co-morbidities (i.e., hypertension, diabetes, or obesity); 19.3% were obese; and 34.1% had evidence of SARS-CoV-2 infection at baseline (defined as detectable IgG antibody to N-protein specific for SARS-CoV-2 rS at Day 0 and/or (+) PCR through Day 21).

- HIV-positive population (n= 244 NVX-CoV2373): all were between 20-60 years of age (median 38 years); 73% were female, 100% were Black; 4.5% were Hispanic/Latino; the medical history included obesity (32.8% of participants), hypertension (6.1% of participants), or diabetes (1.2% of participants); and 34.0% of participants had evidence of SARS-CoV-2 infection at baseline

14.3 Study 2019nCoV-101

Study 101 was designed as a phase 1/2 study to evaluate the safety and immunogenicity of several vaccine and Matrix-M1 adjuvant combinations. The 5 µg SARS-CoV-2 rS + 50 µg Matrix-M formulation was administered to 29 participants 18-59 years of age (part 1; 2 doses) in Australia, and 514 participants 18-84 years of age (part 2; 1 dose or 2 doses [n=257/per dose cohort]) In Australia and the US.

In part 1, the median age was 27 years (range 18, 52), and 50% of participants were female. Eighteen participants (69%) were White, 6 (23%) were Asian, 2 (8%) were American Indian or Alaskan Native; and 6 (23%) were Hispanic/Latino.

In part 2, the median age was 57 years (range 18, 83), and 50% of participants were female. 86% were White, 8% were Asian, and <3% were Black, African American, American Indian or Alaskan Native; 4% were Hispanic/Latino; 52% were from Australia; the median BMI was 26 (17, 35); and 2% of participants had evidence of SARS-CoV-2 infection at baseline.

15. Appendix B. Potential Immune-Mediated Medical Conditions

Table 27. 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 paralyses/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).

Category	Diagnoses (as MedDRA Preferred Terms)
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, morphoea, 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