Vaccines and Related Biological Products Advisory Committee Meeting

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Vaccines and Related Biological Products
FDA Advisory Committee Meeting

NVX-CoV2373 Vaccine for the Prevention of COVID-19

Date: June 7, 2022

Briefing Document

Prepared by

Novavax, Inc. ("Novavax")

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List of Abbreviations

Abbreviation	Term
ACCESS	The vACCine covid-19 monitoring readinESS project
AE	Adverse event
AESI	Adverse event(s) of special interest
AU	Australia
BMI	Body mass index
BP	Blood pressure
CD4	Cluster of differentiation 4 (glycoprotein co-receptor for T-cell receptor)
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Database
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
e-Diary	Electronic diary
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immune absorbent spot
EMA	European Medicines Agency
ERC	Endpoint Review Committee
EU	ELISA units
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FLU-PRO	InFLUenza Patient-Reported Outcome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMT	Geometric mean titer
HAART	Highly active antiretroviral therapy
hACE2	Human angiotensin-converting enzyme 2
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization
IDEA	Independent Data Monitoring Committee and Adjudication
IgG	Immunoglobulin G
IM	Intramuscular
iPSP	initial Pediatric Study Plan
IR	Incidence rate
IRB	Institutional Review Board
LBCI	Lower bound confidence interval
LLOQ	Lower limit of quantification

Abbreviation	Term
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MN	Microneutralization
MX	Mexico (ISO 3166 country code)
n_e	Number of events
NHP	Non-human primates
NVX-CoV2373	5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant
NZW	New Zealand white (rabbit)
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PHEIC	Public health emergency of international concern
PIMMC	Potential immune-mediated medical condition
PP	Per-Protocol
PP-EFF	Per-Protocol Efficacy
PP-IMM	Per-Protocol Immunogenicity
PY	Person-year
r	Recombinant
RD	Risk difference
RR	Relative risk
S	Spike (protein)
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2 rS	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine
SCR	Seroconversion rate
SD	Standard deviation
Sf9	*Spodoptera frugiperda* (insect)
SMC	Safety monitoring committee
SOC	System organ class
Th1	T helper Type 1
Th2	T helper Type 2
UK	United Kingdom
US	United States
VE	Vaccine efficacy
WHO	World Health Organization
ZA	South Africa (ISO 3166 country code)

1 EXECUTIVE SUMMARY

Introduction

Novavax is seeking Emergency Use Authorization (EUA) for an investigational coronavirus disease 2019 (COVID-19) vaccine (NVX-CoV2373) for prevention of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). NVX-CoV2373 is a protein-based vaccine created using Novavax recombinant technology to generate antigen derived from the coronavirus spike (S) protein and is adjuvanted with Novavax's patented saponin-based Matrix-M™ to enhance the immune response and stimulate high levels of neutralizing antibodies. The proposed indication under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in adults ≥ 18 years of age. The proposed dosing regimen is two doses, 0.5 mL each, with each containing 5 μg antigen plus 50 μg Matrix-M adjuvant, administered 3 weeks apart.

This EUA request focuses on safety, efficacy, and immunogenicity data from approximately 30,000 participants in a Phase 3 trial conducted in the United States (US) and Mexico (MX) (Study 2019nCoV-301). In discussions with the FDA, the data and results from the Phase 3 Study 2019nCoV-301 (US/Mexico) have been identified as having the highest relevance for evaluation of NVX-CoV2373 for use in the US and are the primary focus of this briefing document, with only relevant safety data from other studies conducted during the clinical development of the vaccine included [1-7]. The results from this trial, along with additional relevant data from other clinical studies and supporting preclinical studies, indicate that the known and potential benefits of the vaccine outweigh its known and potential risks.

Unmet Need

Despite the wide availability of authorized or approved vaccines, the SARS-CoV-2 pandemic is not well controlled in the US. Globally, some regions have had little access to highly efficacious vaccines. Ongoing viral transmission is supporting the continued emergence of new variants. The predominant variants during 2021 have demonstrated that control of the pandemic depends in large part on increasing global vaccination rates. There remains a need for effective, well-tolerated vaccines with evidence of cross-protection against variant strains. In addition, there remains a desire for vaccines that have been developed using well-understood technology platforms, such as the adjuvanted protein antigen of NVX-CoV2373. NVX-CoV2373 will provide another vaccine option and its availability may help increase vaccination rates and meet the challenges of a continually evolving pandemic.

Storage and transportation of messenger ribonucleic acid (mRNA) vaccines still remains a challenge for developing countries. The proposed 9-month shelf-life of NVX-CoV2373 at 2°C to 8°C simplifies transportation and storage requirements, which may also facilitate reaching vaccination coverage goals.

Key Efficacy Findings from Phase 3 Study 301 (US/Mexico)

The Phase 3 Study 2019nCoV-301 (US/Mexico) is a multi-center, randomized (2:1), observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of NVX-CoV2373 in 29,945 randomized adult participants ≥ 18 years of age, with 25,657 participants included in the Per-Protocol Efficacy (PP-EFF) analysis set. .

The primary endpoint for the study was first occurrence of polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 with onset ≥ 7 days after second dose in serologically negative participants at baseline tested by a single central laboratory. The vaccine was 90.41% protective against the primary endpoint of mild, moderate, or severe disease (Table 1). Efficacy of 100% was observed against the secondary endpoint of moderate or severe illness.

Vaccine efficacy (VE) was generally consistent across key subgroups, though with some differences by ethnicity or age ≥ 65 years (as shown in Figure 9).

Table 1: Study 301 (US/MX): Primary Efficacy Results (PP-EFF Analysis Set)

Parameters	**NVX-CoV2373 (N=17,272)**	**Placebo (N=8,385)**
Cases	17 (0.098%)	79 (0.942%)
Mild	17	66
Moderate	0	9
Severe	0	4
Vaccine Efficacy: *Overall*	90.41% (95% CI: 83.81, 94.32)	
Vaccine Efficacy: *Moderate/Severe*	100.0% (95% CI: 85.41, 100.00)	

Abbreviations: CI = confidence interval; PP-EFF = Per-Protocol Efficacy.
Note: Data shown are based on the 27 September 2021 data cutoff date.

Efficacy was also demonstrated against non-Variants of Concern or Interest (which were closely matched to the prototype vaccine strain) and Variants of Concern or Interest. Vaccine efficacy (VE) overall was 97% for viruses most closely resembling the prototype SARS-CoV-2 strain from which the vaccine antigen was derived, and 93% for Variants of Concern or Interest in circulation during the time that the study was conducted.

As part of this study, participants were subsequently crossed over in a blinded fashion after their initial two-dose vaccination series to receive either two doses of placebo or two doses of vaccine.

Safety Findings

Safety assessments in the NVX-CoV2373 clinical studies included monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), vital sign measurements, and physical

examinations. Safety data are available for both the pre-crossover and post-crossover vaccination periods as of the data cutoff date of 27 September 2021. For the initial vaccination period (pre-crossover), median follow-up post Dose 2 was 2.5 months with 77.6% of participants in the NVX-CoV2373 group and 72.8% of participants in the placebo group being followed for at least 2 months post-Dose 2. For the blinded crossover vaccination period (post-crossover), median follow-up post Dose 4 was 4.4 months with approximately 99% of participants being followed for at least 2 months post Dose 4.

Solicited Local Adverse Events

Solicited local AEs were recorded by participants in a diary from the start of each study vaccination until 7 days after each study vaccination. Solicited local AEs consisted of pain/tenderness, erythema, and swelling. A greater proportion of participants in the NVX-CoV2373 group reported solicited AEs following each vaccination compared to the placebo group (Figure 11). In the NVX-CoV2373 group, the frequency and intensity of solicited local AEs increased after second vaccination relative to the first vaccination; most participants in the NVX-CoV2373 group reported mild or moderate solicited local events following each vaccination. Frequencies of severe events (Grade 3+) were relatively low (< 10%), but such events generally occurred more frequently in the NVX-CoV2373 group than in the placebo group. Grade 4 events were reported in few participants (< 1.0%) in either group and were primarily participant-reported events that were miscategorized through data entry error by the participants in their e-diary. The most frequent solicited local AEs following each vaccination was pain/tenderness, which had a median duration of 1.0 day.

Solicited Systemic Adverse Events

Solicited systemic AEs were recorded by participants in a diary from the start of each study vaccination until 7 days after each study vaccination. Solicited systemic AEs consisted of headache, fatigue/malaise, muscle pain, joint pain, fever, and nausea or vomiting. Similar to solicited local AEs, there were higher frequencies of systemic AEs among NVX-CoV2373 recipients than among placebo recipients following each vaccination (Figure 12). The frequency and intensity of solicited systemic AEs increased after second vaccination, relative to the first vaccination in the NVX-CoV2373 group. Most events in the NVX-CoV2373 group were mild or moderate in intensity. Frequencies of severe events were relatively low (< 15%), but greater in the NVX-CoV2373 group than in the placebo group. Grade 4 events were reported in few participants (< 1.0%) in either group and were patient-reported events that mostly were acknowledged as data entry errors by participants in the e-diaries. The most frequent (incidence > 20.0% after each vaccination) solicited systemic AEs following each vaccination were fatigue, muscle pain, and headache. Solicited systemic events were of short duration, with a median duration of 1.0 day.

As expected, a comparison of age groups (18 to 64 and ≥ 65 years) shows that participants in the older age cohort reported a lower frequency and intensity of solicited systemic AEs than participants in the younger age cohort.

Unsolicited Adverse Events

Unsolicited AEs were recorded from after the start of first vaccination through 28 days after second vaccination (ie, Day 49). The overall frequency of unsolicited non-serious AEs were balanced between the NVX-CoV2373 and placebo groups (11.6% vs 11.2%, respectively). The rates of medically attended AEs (MAAEs), severe AEs, SAEs, and potential immune-mediated medical conditions (PIMMCs) were low and were relatively balanced between groups.

Deaths

In the pooled analysis of safety data from all clinical studies, the overall mortality rate was balanced between study arms. A total of 11 (< 0.1%) participants in the NVX-CoV2373 group and 5 (< 0.1%) participants in the placebo group died during the pre-crossover period (Table 15). Frequencies were similarly low and balanced during the post-crossover period. None of the deaths were assessed by either the investigator or Sponsor as related to trial vaccine.

Safety Events of Interest

To date, no cases of anaphylactic reactions or thrombosis with thrombocytopenia have been reported in participants receiving NVX-CoV2373 in the clinical development program. Recent follow-up on one case of neuropathy in a vaccine recipient from Study 302 (Phase 3, United Kingdom [UK]) provided details that met the Brighton Collaboration case definition for Guillain-Barré syndrome.

An analysis of cholecystitis noted a higher incidence of serious events of cholecystitis or acute cholecystitis in vaccine recipients compared to placebo during the pre-crossover period. However, the overall frequency was low, and the risk difference between treatment groups was also low. Event rate per 100 PY was higher in vaccine recipients (0.16) than placebo recipients (0.04) with a risk difference (RD) in rate per 100 PY of 0.07 (95% CI: 0.00, 0.14). However, the upper bound of the 95% CI of adverse events was within the background rate of 0.12 to 0.35 cases/100 PY. The totality of evidence, including the presence of risk factors and the time to onset of cases, did not suggest a causal relationship.

In the pre-crossover period, myocarditis/pericarditis events were balanced across the NVX-CoV2373 and placebo groups: 2 events (0.007%) in NVX-CoV2373 and 1 event (0.005%) in placebo. When evaluated with an exposure-adjusted incidence rate per 100 PY, myocarditis/pericarditis cases in the NVX-CoV2373 group occurred at 0.03 events/100 PY compared with 0.02 events/100 PY in the placebo group with a statistical RD of 0.00 (95% CI: -0.06, 0.07). The observed rate of 3 cases/14,513 PY of myocarditis/pericarditis during the post-crossover period was within the range of expected background cases based on data from ACCESS, a study funded by the European Medicines Agency to determine background rates for COVID-19 vaccine AESIs.

Safety Conclusions

The safety data from the clinical program supports a positive benefit-risk profile which includes a favorable reactogenicity profile. Safety was well-characterized via exposure in > 40,000 recipients of the vaccine at the proposed dose level and dosing interval across all clinical studies. Local and systemic events were generally mild to moderate in intensity and of short duration. Most AEs were mild to moderate severity, and SAE rates in the NVX-CoV2373 group were low and comparable to placebo. In addition, there were no clinically significant safety signals for AESIs or other safety events of interest.

Benefit-Risk Summary

The totality of the data across the clinical development program for NVX-CoV2373 demonstrates that it is a highly effective vaccine with an acceptable safety profile for prevention of COVID-19 caused by SARS-CoV-2 infection.

NVX-CoV2373 uses a well-established vaccine technology platform, including a recombinant spike protein antigen with a saponin adjuvant derived from a natural product. In addition, NVX-CoV2373 offers a reassuring safety profile and favorable reactogenicity profile. NVX-CoV2373 may provide an important option to increase vaccine uptake, including in populations reluctant to utilize newer technologies, and thereby diminish the severe disease and hospitalizations caused by SARS-CoV-2. Considering the ongoing public health emergency due to SARS-CoV-2 and its emerging variants, the need for additional effective vaccines, and the available efficacy, immunogenicity, and safety data across the NVX-CoV2373 clinical development program, the Sponsor considers that the known and potential benefits of the vaccine outweigh its known and potential risks and warrant consideration for authorization in individuals 18 years of age and older.

2 BACKGROUND ON SARS-COV-2 AND COVID-19

Summary

- Current vaccine options in the US are limited to two mRNA vaccines and one non-replicating, viral vector-based vaccine (with a newly restricted indication).
- Despite these options, 24% of adults in the US are not fully vaccinated.
- Variants continue to emerge as vaccine rates remain low in many countries.
- There remains an unmet clinical need for vaccines that are: highly efficacious, well tolerated, have well-understood technology platforms, and allow for ease of distribution and storage.

2.1 COVID-19 and Pandemic Background

In late December of 2019, an outbreak of respiratory disease caused by novel coronavirus (2019-nCoV) was detected in Wuhan, Hubei province, China. The rapidly discerned genetic relationship of the virus with the 2002-2003 SARS-CoV resulted in adoption of the name "SARS-CoV-2" for the virus, with the disease being referred to as "COVID-19." Despite containment efforts following the start of the outbreak, SARS-CoV-2 spread rapidly across the globe [8]. On 30 January 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) designated the outbreak as a public health emergency of international concern (PHEIC), and subsequently declared a pandemic on 11 March 2020. By early May 2022, approximately 515 million cases of COVID-19 had been confirmed globally, including approximately 6.3 million related deaths [9].

2.2 Current Vaccine Landscape

Three COVID-19 vaccines have been approved or authorized for emergency use by the US Food and Drug Administration (FDA) for active immunization to prevent COVID-19:

- The Pfizer-BioNTech mRNA-based BNT162b2 vaccine is approved for individuals 16 years of age and older as a primary series of two doses of 0.3 mL each and authorized for individuals between the ages of 5 to 15 years as a primary series of two doses of 0.2 mL each.

- The Moderna, Inc. mRNA-1273 vaccine has been authorized for emergency use in individuals 18 years of age and older as a primary series of two doses of 0.5 mL each.

- The Johnson & Johnson (J&J)/Janssen Ad26.COV2.S vaccine is the only non-mRNA vaccine for COVID-19 currently available in the US. While this vaccine was previously authorized for emergency use in individuals 18 years of age and older as a single dose of

0.5 mL, the authorization has recently been revised because of emerging safety concerns to limit use only to individuals for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the J&J/Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine.

2.3 Emerging Variants

New genetic variants of SARS-CoV-2 began emerging and spreading in late 2020, including variants first identified in the UK (referred to as Alpha or B.1.1.7), South Africa (Beta or B.1.351), and Brazil (Gamma or P.1). Some variants may be able to spread more quickly or be resistant to vaccine-induced immunity [10].

Since it emerged in mid-November 2021, variant of concern Omicron (or B.1.1.529) quickly became the dominant variant in many parts of the world, including the US [11]. Subsequently, other lineages of the Omicron variant have spread; as of 07 May 2022, lineage BA.2 had become the most common source of COVID-19 infections in the US, comprising approximately 56% of cases, with lineage BA.2.12.1 comprising approximately 43% of cases [12]. Based on epidemiologic data, Omicron appears to be more contagious than the Delta variant (or B.1.617.2 and AY lineages) and the prototype strain. In addition, Omicron is more likely than Delta to reinfect individuals who previously had COVID-19 and more likely to infect others regardless of vaccination status [13].

It is generally agreed that more variants will emerge, and the virus will not become endemic like the flu as long as global vaccination rates remain low. WHO Director General Tedros Adhanom Ghebreyesus has said that protecting people from future variants, including those that may be fully resistant to today's shots, depends on ending global vaccine inequity. The WHO has a stated goal of having 70% of people in every country vaccinated by mid-2022 [14].

Currently in the US, as of mid-May 2022, approximately 78% of the population have received at least one dose of a COVID-19 vaccine, with 67% of the total population fully vaccinated, and approximately 83% of the population ≥ 5 years of age have received at least one dose of a COVID-19 vaccine [15].

2.4 Unmet Need

Despite the increased availability of authorized or approved vaccines, the SARS-CoV-2 pandemic is not well controlled in the US. Globally, some regions have had little access to highly efficacious vaccines. Ongoing viral transmission is supporting the continued emergence of new variants. The predominant variants during 2021-2022 have demonstrated that control of the pandemic depends in large part on increasing global vaccination rates. There remains a need for effective, well-tolerated vaccines with evidence of cross-protection against variant strains. In addition, there remains a desire for vaccines that have been developed using well-understood

technology platforms, such as the adjuvanted protein antigen of NVX-CoV2373. NVX-CoV2373 will provide another vaccine option and its availability may help increase vaccination rates.

The need for additional vaccines in the US armamentarium is evidenced by the approximately 24% of adult Americans (as of mid-May 2022) who are not yet fully vaccinated. Severe cases of COVID-19 requiring hospitalization have occurred disproportionately among unvaccinated individuals, and this circumstance is currently a driver of overwhelming demands on the US healthcare system. This demand causes a cycle of over-burdening our healthcare providers and facilities and creates risk for people who need medical care for other serious conditions. An additional highly efficacious vaccine with a reassuring safety profile may help address the need to increase vaccination rates.

Storage and transportation of mRNA vaccines still remains a challenge for developing countries. The proposed 9-month shelf-life of NVX-CoV2373 at 2°C to 8°C simplifies transportation and storage requirements which may also help in reaching vaccination coverage goals.

3 NOVAVAX COVID-19 VACCINE (NVX-COV2373) PRODUCT DESCRIPTION

Summary

- NVX-CoV2373 is a protein-based vaccine engineered from the genetic sequence of SARS-CoV-2, the virus that causes COVID-19.
- NVX-CoV2373 was created using Novavax recombinant technology to generate antigen derived from the coronavirus S protein and is adjuvanted with Novavax's patented saponin-based Matrix-M to enhance the immune response and stimulate high levels of neutralizing antibodies.
- NVX-CoV2373 contains purified protein antigen and can neither replicate, nor can it cause COVID-19.

3.1 Proposed Indication

NVX-CoV2373, administered intramuscularly as a series of two doses (0.5 mL each, with each containing 5 μg antigen plus 50 μg Matrix-M adjuvant) 3 weeks apart, is indicated for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in adults ≥ 18 years of age.

3.2 Product Overview

NVX-CoV2373 is a protein-based vaccine engineered from the genetic sequence of SARS-CoV-2 Wuhan-Hu-1 strain, the virus that initiated the COVID-19 pandemic. NVX-CoV2373 was created using Novavax recombinant technology to generate antigen derived from the coronavirus S protein and is adjuvanted with Novavax's patented saponin-based Matrix-M to enhance the immune response and stimulate high levels of neutralizing antibodies. NVX-CoV2373 contains purified protein antigen, cannot replicate, and cannot cause COVID-19.

NVX-CoV2373 is supplied in 10-dose vials. The product should be stored at 2°C to 8°C, protected from light, and should ***not*** be frozen. Each dose is injected in a volume of 0.5 mL and contains 5 μg antigen plus 50 μg Matrix-M adjuvant. No reconstitution or dilution is required.

3.3 Product Components and Mechanism of Action

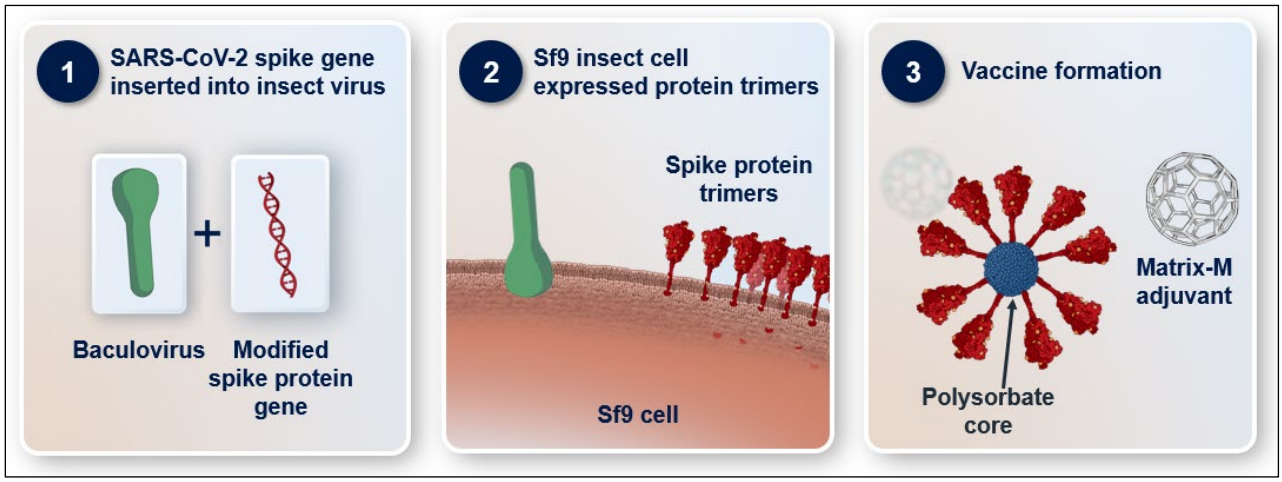
The NVX-CoV2373 vaccine design includes these components:

- NVX-CoV2373 begins with the full-length, pre-fusion stabilized SARS-CoV-2 spike protein (prototype Wuhan-Hu-1 strain). That sequence is engineered into a baculovirus.
- The recombinant baculovirus infects the *Spodoptera frugiperda*, or Sf9, insect cell expression system.

- When the baculovirus enters the Sf9 cell nucleus, the S gene is transcribed into mRNA, which is then translated in the Sf9 cell cytoplasm, where post-translational modifications ultimately produce full-length S in its native trimer conformation.
- S trimers are purified from the insect cells; their native transmembrane domains enable them to be embedded in a Polysorbate 80, or PS80, core, forming vaccine particles, preserving the native structure.
- The final vaccine is formulated when vaccine particles are mixed with Novavax's Matrix-M adjuvant, creating the ready-to-use liquid that is stable at 2°C to 8°C. The vaccine's recombinant protein particles mimic the virus' surface S proteins and stimulate immunity but are not infectious and expose the recipient to only 5 µg of S protein.

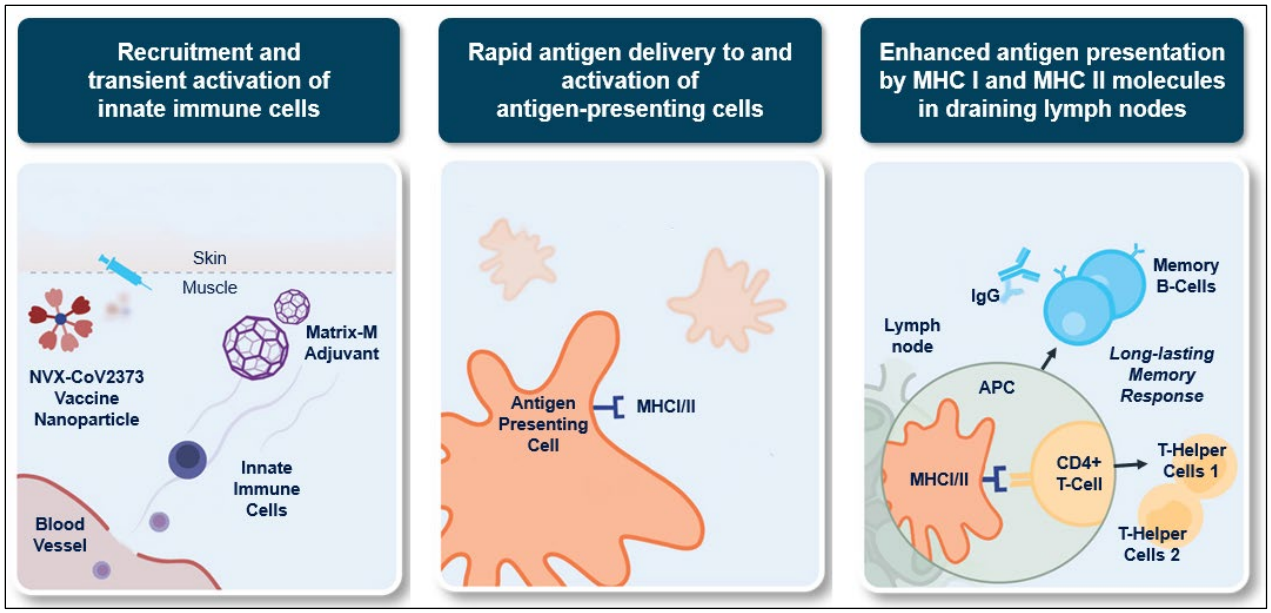
The process is illustrated in Figure 1 (antigen recombinant S protein) and Figure 2 (Matrix-M adjuvant effect on immune response), and additional details regarding the product components are provided below.

Figure 1: NVX-CoV2373 Vaccine Design: Antigen Full Length Recombinant Spike Protein



Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Sf9 = *Spodoptera frugiperda*

Figure 2: Matrix-M Adjuvant Effect on Immune Response



Abbreviations: APC = antigen presenting cell; CD4 = cluster of differentiation 4 (glycoprotein co-receptor for T-cell receptor); IgG = immunoglobulin G; MHC = major histocompatibility complex; Sf9 = *Spodoptera frugiperda*

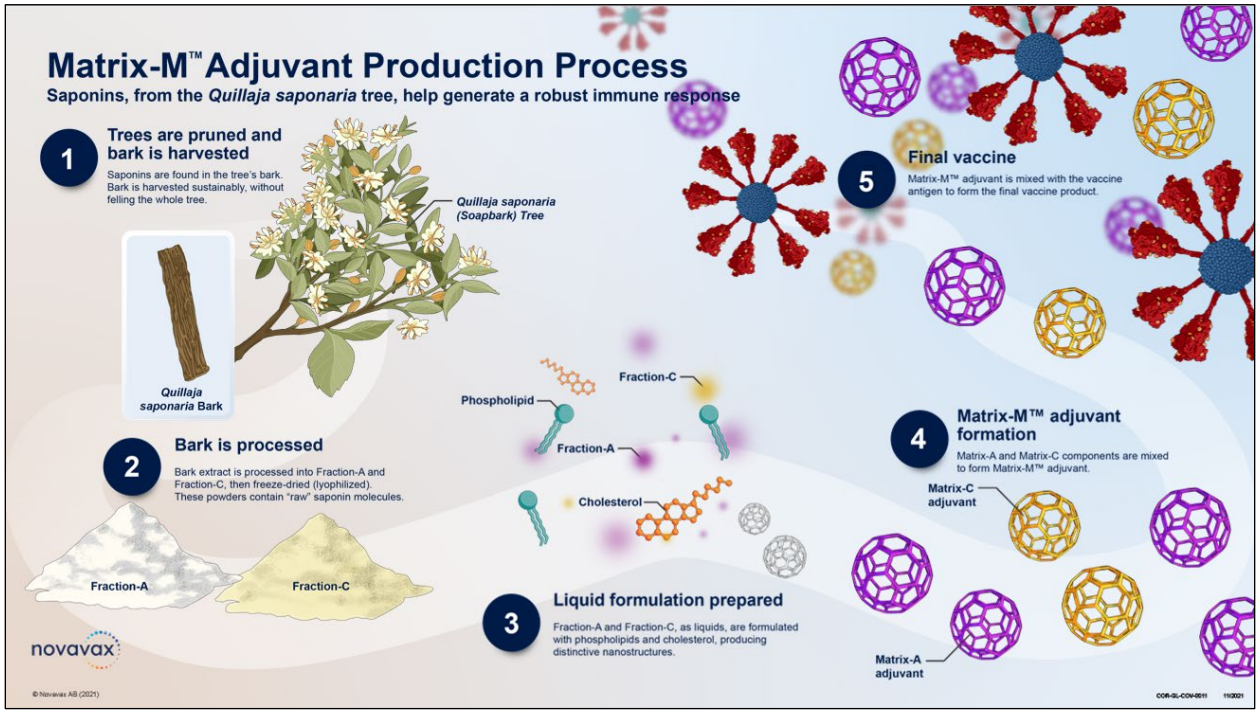
3.3.1 Recombinant Protein Antigen

NVX-CoV2373 comprises the recombinant S protein of SARS-CoV-2 (SARS-CoV-2 rS) co-formulated with the saponin-based Matrix-M adjuvant and is constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein based upon the GenBank gene sequence MN908947 (Wuhan-Hu-1 isolate) nucleotides 21563-25384. The S protein is a Type 1 trimeric glycoprotein of 1273 amino acids that is produced as an inactive S0 precursor. To produce the SARS-CoV-2 rS vaccine candidate, the S gene was codon optimized for expression in Sf9 insect cells. The native full-length S protein was modified to be protease resistant. Two additional proline amino acid substitutions were inserted to stabilize SARS-CoV-2 S in a pre-fusion conformation, which is believed to optimize presentation of neutralizing epitopes [16]. The synthetic transgene has been engineered into the baculovirus vector for expression in Sf9 insect cells. Purified SARS-CoV-2 rS protein trimers are uncleaved, thermostable at elevated temperatures (maximum temperature > 60ºC), and specifically bind the human angiotensin-converting enzyme 2 (hACE2) receptor, the receptor used by SARS-CoV-2 to attach to human cells, with high affinity [17]. The candidate vaccine contains the 3Q and 2P mutations [18] and is designated as SARS-CoV-2 rS.

3.3.2 Matrix-M Adjuvant Technology

The production of Matrix-M adjuvant is illustrated in Figure 3.

Figure 3: Matrix-M Adjuvant Production Process



The mode of action of Matrix-M adjuvant has been studied in different animal models, and a similar saponin-based adjuvant has been FDA-approved for other vaccines, including the herpes zoster (shingles) vaccine. Matrix-M adjuvant induces a rapid, local, and transient activation of innate immune cells including upregulation of cytokine and chemokine levels. The adjuvant effects are substantially limited in both time and space to the time and site of the vaccine injection. For an adjuvant effect to occur, Matrix-M adjuvant and the antigen of interest need to be delivered to the same site, and likely targeting the same draining lymph node, within a relatively short temporal window. Cytokine and chemokine generation peaks 6 to 48 hours after injection with a subsequent rapid decrease at 72 hours and return to background levels by 168 hours, illustrating the rapid and transient nature of the response.

The Matrix-M adjuvant is derived from fractionated *Quillaja saponins*, phosphatidylcholine, and cholesterol. It has been shown to enhance the immunogenicity of nanoparticle vaccines in nonclinical and clinical studies [1, 17, 19, 20].

In summary, the Matrix-M adjuvant induces a well-characterized and robust immune response that results in long-term immunity.

3.4 Therapeutic Rationale Supporting Investigation: Nonclinical Studies

Key findings from the nonclinical studies for NVX-CoV2373 are summarized in Figure 4 and described in more detail below.

Figure 4: NVX-CoV2373 Nonclinical Results Supporting Clinical Development

Types of studies	Key findings
Immunogenicity	▪ Induced anti-spike IgG, hACE2-binding inhibiting antibodies, and neutralizing antibodies ▪ Induced strong Th1-type CD4+ T-cell responses
Animal challenge	▪ Suppressed viral replication in both upper and lower airways ▪ No evidence of enhanced disease pathology
Toxicology	▪ No safety concerns identified in standard toxicology program ▪ No adverse findings in developmental and reproductive toxicology study

Abbreviations: CD4 = cluster of differentiation 4 (glycoprotein co-receptor for T-cell receptor); IgG = immunoglobulin G; hACE2 = human angiotensin-converting enzyme 2; Th1 = T Helper Type 1

3.4.1 Nonclinical Immunogenicity and Efficacy

NVX-CoV2373 has been demonstrated to induce both a cellular and humoral immune response across multiple species, including rodents and non-human primates (NHPs). NVX-CoV2373 elicited rapid and robust humoral immune responses as measured by anti-S immunoglobulin G (IgG), hACE2 receptor binding inhibiting, and wild-type virus neutralizing antibodies, which were increased with the addition of adjuvant (versus antigen alone) and following a second vaccine administration (versus a single dose). In NHP models, two human doses of 5 or 25 µg NVX-CoV2373 resulted in maximal immune responses with no notable differences between the two antigen doses. Importantly, in mice and NHP models, NVX-CoV2373 also induced strong T Helper Type 1 (Th1)-type cluster of differentiation 4 positive (CD4+) T-cell responses, which included polyfunctional effector phenotypes, and demonstrated a balanced Th1/T helper Type 2 (Th2) response phenotype based on both patterns of antigen-specific stimulated cytokine production and, in mice, specific IgG1/IgG2a ratios. In addition, Matrix-M adjuvant-associated enhancement of splenic T follicular helper and germinal center B-cell populations suggests favorable conditions for establishment of a diverse, high affinity, and durable antibody response.

Live virus challenge studies were performed in mice, hamsters, cynomolgus macaques, and rhesus macaques. In mouse challenge models, immunization with NVX-CoV2373 suppressed viral replication, reduced lung inflammation, and reduced systemic morbidity (weight loss) after SARS-CoV-2 live virus challenge and was not associated with any obvious exacerbation of the

inflammatory response to the virus or worsening of clinical outcomes. Similar protection from weight loss, reduced activity level, viral replication, and lung histopathology following live virus challenge was observed in hamsters. In cynomolgus and rhesus macaques, animals immunized with two-dose regimens of NVX-CoV2373 at the proposed human dose were maximally protected against live virus challenge as evidenced by protection against viral replication in the upper and lower airways.

Taken together, these data indicate that immunization with NVX-CoV2373 elicits the generation of functional antibodies against the SARS-CoV-2 S protein in vivo, which are capable of blocking binding of the S protein to its native receptor (hACE2) and preventing viral infection of cells; thus, demonstrating the potential to prevent infection with the virus. Notably, animals across multiple species vaccinated with NVX-CoV2373 were protected from viral replication in the upper and lower respiratory tract following challenge with live SARS-CoV-2. Cellular immune responses induced by NVX-CoV2373 were generally Th1-dominant. Importantly, no evidence of vaccine-associated enhanced respiratory disease via histopathological evaluation of the lungs following live virus challenge has been observed in any study.

3.4.2 Nonclinical Safety

A standard toxicology program to support vaccine development has been undertaken for NVX-CoV2373 with no adverse findings identified to date. A Good Laboratory Practice (GLP) compliant repeat-dose toxicity study conducted in New Zealand white (NZW) rabbits demonstrated NVX-CoV2373 was well tolerated with no adverse findings. In addition, the totality of toxicology data obtained in rat and rabbit GLP studies, which have evaluated Matrix-M adjuvant alone or co-administered with different vaccine antigens, has failed to demonstrate overt systemic or organ-specific toxicities and Matrix-M adjuvant administration was generally well tolerated. Local injection site inflammation and regional lymph node hyperplasia consistent with active immunization were present in acute necropsies but showed resolution during recovery. Similarly, biochemical markers of inflammation, such as elevated globulins, fibrinogen, and C-reactive protein (CRP), were present acutely after dosing but tended to resolve prior to the next vaccine exposure or during recovery. In addition, data from a developmental and reproductive toxicity study in rats has shown no adverse findings to date for NVX-CoV2373 or Matrix-M adjuvant alone. Lastly, pilot non-GLP *in vitro* genotoxicity studies indicated that Matrix-M adjuvant is non-mutagenic; and this was confirmed in GLP-compliant *in vitro* genotoxicity studies in bacteria and mammalian cells.

3.4.3 Nonclinical Studies: Conclusions

In conclusion, nonclinical studies have demonstrated that NVX-CoV2373 generates a robust and functional immune response, eliciting neutralizing antibodies against SARS-CoV-2, resulting in protective efficacy following live viral challenge across multiple species. No adverse risks have been identified in the nonclinical testing program to date, and the data support the proposed dose and regimen for human use (ie, 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant administered on Days 0 and 21). Studies across multiple species immunized with

NVX-CoV2373, including NHP models administered the intended human dose, have shown no evidence of vaccine-enhanced disease following challenge with live SARS-CoV-2 virus, even when administered at suboptimal vaccine doses (ie, single doses and/or lower antigen/adjuvant doses). In the GLP repeat-dose toxicity study, 50 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant was well tolerated with non-adverse findings limited to local injection site inflammation and serum chemical markers of inflammation, which were transient and considered consistent with immune system stimulation consequent to immunization. Data from a GLP developmental and reproductive toxicity study in rats indicates no adverse effects on fertility or reproductive performance in F_0 females or survival or fetal or post-natal development in F_1 pups. Taken as a whole, the nonclinical data supported evaluation of both 5 and 25 µg SARS-CoV-2 rS doses with and without Matrix-M adjuvant in the clinical development program.

4 REGULATORY AND CLINICAL DEVELOPMENT OVERVIEW

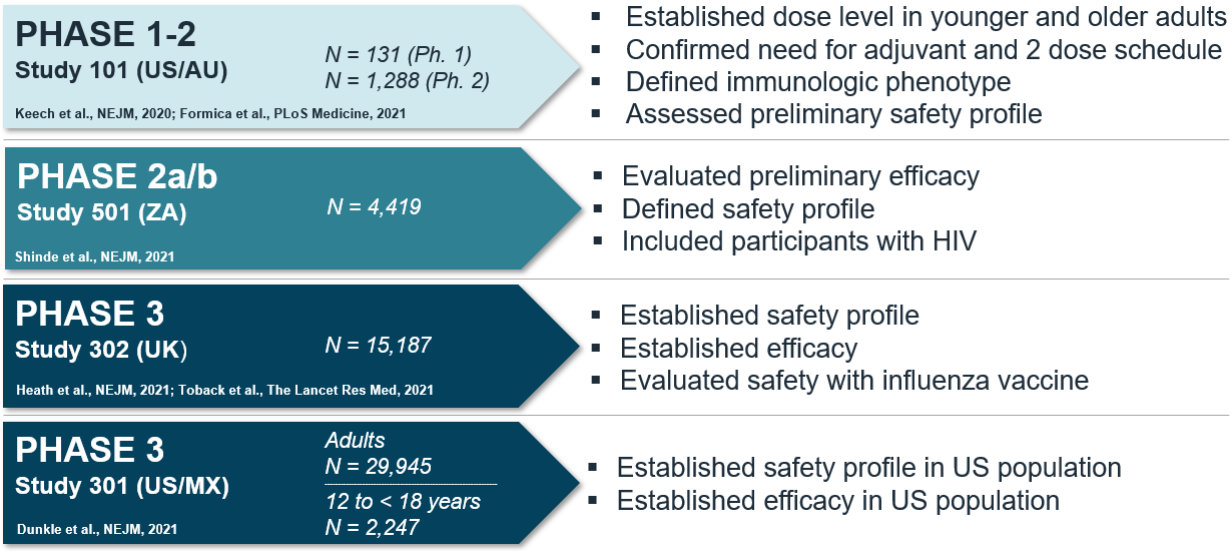
4.1 Regulatory Overview

The NVX-CoV2373 clinical program was conducted following the Good Clinical Practice (GCP) principles as outlined in International Council for Harmonization (ICH) E6 (R2). In addition, Novavax developed the program in accordance with the emerging global guidelines for COVID-19 vaccine development, including, but not limited to, those issued by the US FDA, the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), and WHO.

4.2 Clinical Development Program: Initiated and Ongoing Studies

The clinical development program for NVX-CoV2373 is illustrated in Figure 5. A descriptive overview of the four clinical studies of NVX-CoV2373 that are included in the EUA application is provided in Table 2. Safety data from all of the studies are part of the EUA application, while efficacy and immunogenicity data are derived from the largest, US/Mexico, Phase 3 study 2019nCoV-301 only.

Figure 5: NVX-CoV2373 Clinical Development Program



Abbreviations: AU = Australia; HIV = human immunodeficiency virus; MX = Mexico; N = number of participants randomized; Ph = Phase; UK = United Kingdom; US = United States; ZA = South Africa

References:

Phase 1-2 Study 2019nCoV-101 (US/AU): [5, 6]

Phase 2a/b Study 2019nCoV-501 (ZA): [1]

Phase 3 Study 2019nCoV-302 (UK): [3, 4]

Phase 3 Study 2019nCoV-301 (US/MX): [21]

Table 2: Overview of Initiated/Ongoing Clinical Studies of NVX-CoV2373

Study Identifier/ Phase/ Status	Countries	Study Objective(s)	Study Design	Participant Population/ Number	Dose/Dosing Regimen
Title: A 2-Part, Phase 1/2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With or Without Matrix-M Adjuvant in Healthy Subjects					
Study 2019nCoV-101 Abbreviation: Study 101 (AU/US) Phase 1/2 Phase 1 completed; Phase 2 ongoing	US and Australia	To assess safety and immunogenicity	Randomized, parallel assignment, observer-blinded, placebo-controlled	Healthy adult males or females between 18 and 59 years of age (Phase 1) and 18 and 84 years of age (Phase 2) Randomized: 134 (Part 1), with 131 dosed; 1,288 (Phase 2), with 1,283 dosed	Phase 1: 5 or 25 µg SARS-CoV-2 rS mixed with or without 50 µg Matrix-M adjuvant, 0.6 or 0.5 mL) or placebo on Days 0 and 21; Phase 2: 5 or 25 µg SARS-CoV-2 rS coformulated with 50 µg Matrix-M adjuvant, 0.5 mL) on Days 0 and 21 (Initial Vaccination Period) and on Days 189 and 357 (booster vaccinations in subset only)
Title: A Phase 2a/b, Randomized, Observer-blinded, Placebo-controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1 Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in Adults Living With HIV					
Study 2019nCoV-501 Abbreviation: Study 501 (ZA) Phase 2a/b Ongoing	South Africa	To assess efficacy, immunogenicity, and safety	Randomized, sequential assignment, blinded, placebo-controlled	Healthy HIV-negative adults 18 to 84 years and medically stable PLWH adults 18 to 64 years at screening. Randomized: 4,419, with 4,408 dosed	NVX-CoV2373 (5 µg SARS-CoV-2 rS – + 50 µg Matrix-M adjuvant administered as a coformulation, 0.5 mL) or placebo, 1 dose each on Days0 and 21 (Initial Vaccination Period) and on Day 201 (single booster vaccination) for participants randomized to active vaccine; placebo recipients received active vaccine on Days 201 and 222 in a blinded crossover period.

Table 2: Overview of Initiated/Ongoing Clinical Studies of NVX-CoV2373

Study Identifier/ Phase/ Status	Countries	Study Objective(s)	Study Design	Participant Population/ Number	Dose/Dosing Regimen
Title: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1 Adjuvant in Adult Participants 18-84 Years of Age in the United Kingdom					
Study 2019nCoV-302 Abbreviation: Study 302 (UK) Phase 3 Ongoing	UK	To assess efficacy, safety, and immune response	Randomized, parallel assignment, observer-blinded, placebo-controlled	Adults 18 to 84 years Randomized: 15,187, with 15,139 dosed (4,125 ≥ 65 years old dosed)	NVX-CoV2373 (5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant administered as a coformulation, 0.5 mL) or placebo on Days 0 and 21, and 1 IM injection of licensed seasonal flu vaccine on Day 0; placebo recipients received active vaccine in a blinded crossover period approximately 3 months after primary vaccination.
Title: 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					
Study 2019nCoV-301 Abbreviation: Study 301 (US/MX) Phase 3 Ongoing	US and Mexico	To assess efficacy, safety, and immune response	Randomized, observer-blinded, placebo-controlled; blinded crossover implemented after median 60-day safety follow-up	Adults ≥ 18 years of age at screening who, by virtue of age, race, ethnicity or life circumstances, are considered at substantial risk of exposure to and infection with SARS-CoV-2. Randomized: 29,945, with 29,582 dosed (3,715 ≥ 65 years old dosed)	NVX-CoV2373 (5 µg SARS-CoV-2 rS + 50 µg Matrix-M adjuvant administered as a coformulation, 0.5 mL) or placebo, 1 dose of the assigned product on Days 0 and 21 (Initial Vaccination Period); 1 dose of the alternate material on Day 0 and Day 21 (Crossover Vaccination Period).

Abbreviations: AU = Australia; HIV = human immunodeficiency virus; MX = Mexico; NVX-CoV2373 = 5 µ SARS-CoV-2 rS + 50 µg Matrix-M adjuvant; PLWH = people living with HIV; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; UK = United Kingdom; US = United States; ZA = South Africa

4.3 Clinical Development Program: Additional and Planned Studies

4.3.1 Pediatric

In May 2021, a pediatric expansion was added to Study 301 (US/MX) to evaluate the efficacy, effectiveness, safety, and immunogenicity of NVX-CoV2373 in up to 3,000 adolescents aged 12 to < 18 years across up to 75 sites in the US. Unblinded safety and efficacy data from the pediatric expansion are reviewed monthly by the Data and Safety Monitoring Board (DSMB). Results from the pediatric expansion have been made publicly available and are currently under review by Regulators outside of the US [22].

In addition to the pediatric expansion for Study 301 (US/MX), an initial Pediatric Study Plan (iPSP) describing the further plans for pediatric development has been submitted to the FDA and received approval.

4.3.2 Omicron Variant Study

Novavax is developing a monovalent Omicron-based SARS-CoV-2 vaccine as well as a bivalent vaccine and is conducting a study to gather data that may support approval of the vaccine(s) if it is determined that there is a public health need for the vaccine(s).

4.3.3 Other Studies

Novavax is conducting an ongoing additional study in individuals living with human immunodeficiency virus (HIV) that is evaluating a three-dose initial vaccine regimen as well as alternative dosing intervals.

5 CLINICAL IMMUNOGENICITY

Summary

- NVX-CoV2373 (5 µg antigen dose with 50 µg adjuvant dose) confirmed for late-stage development.
- Induces robust anti-S IgG, and neutralizing antibodies against wild-type virus at levels that exceed convalescent sera.
- Induces polyfunctional Th1-biased T-cell response.

5.1 Introduction

Nonclinical immunogenicity is described in Section 3.4.1.

Clinical immunogenicity was a secondary endpoint in Study 301 (US/MX).

Humoral immunogenicity assays included assessments for IgG antibody to SARS-CoV-2 S protein by enzyme-linked immunosorbent assay (ELISA), neutralizing antibodies by microneutralization (MN) using wild-type virus, and hACE2 receptor binding inhibiting antibodies by an inhibition assay.

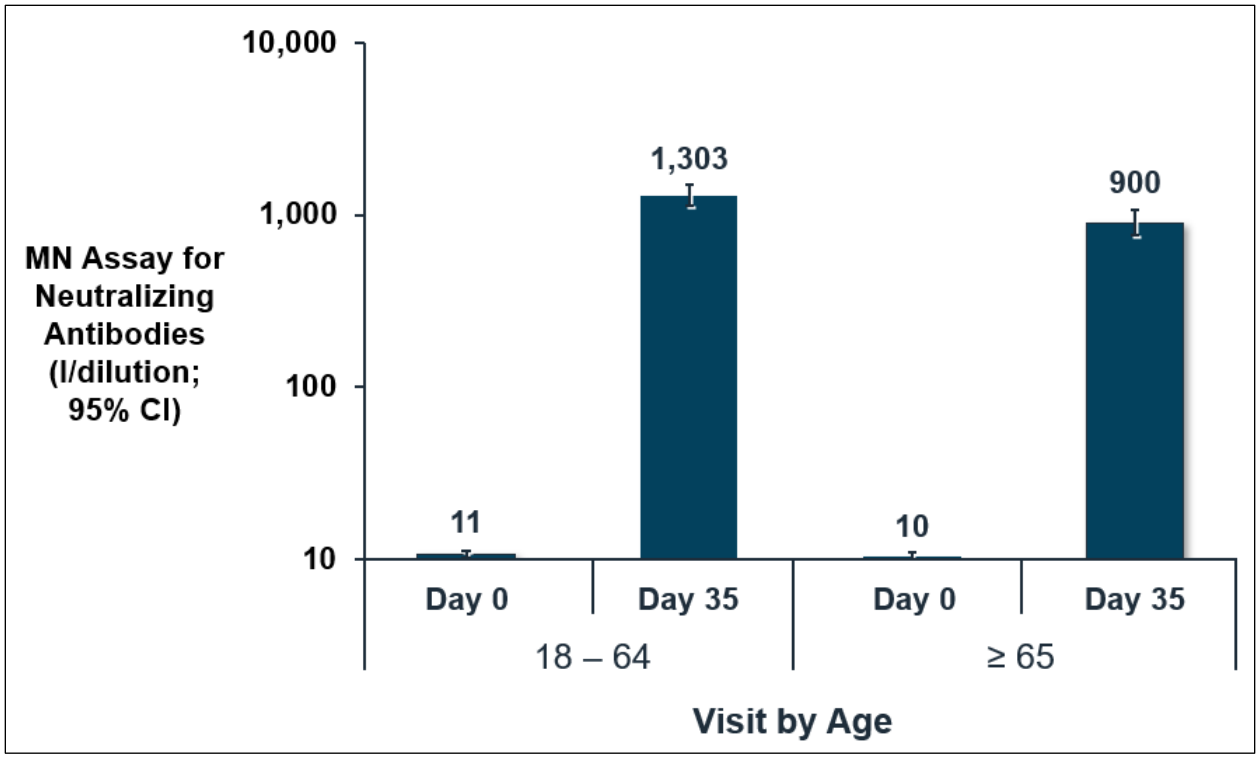
Cellular immunogenicity assays included whole blood (flow cytometry) and/or *in vitro* peripheral blood mononuclear cell (PBMC) stimulation (eg, enzyme-linked immune absorbent spot [ELISpot], cytokine staining) [5].

5.2 Phase 3 Study 2019nCoV-301 (US/MX): Immunogenicity

Study 301 (US/MX) is a randomized, observer-blinded, placebo-controlled Phase 3 trial to evaluate the efficacy, immunogenicity, and safety of NVX-CoV2373. The randomization ratio was 2:1 vaccine to placebo. Immunogenicity data were analyzed as of the data cutoff date of 27 September 2021 (data extraction date of 17 February 2022). Additional details on the design of Study 301 (US/MX) are provided in Section 6.1.1.

A two-dose regimen of NVX-CoV2373, administered 21 (+ 7) days apart, markedly increased neutralizing antibody levels relative to placebo in adult participants ≥ 18 years of age were seronegative to SARS-CoV-2 at baseline (Figure 6); similar robust responses were seen for serum IgG antibody. At 2 weeks following second vaccination (Day 35), neutralizing antibody GMTs in the NVX-CoV2373 group were markedly increased relative to baseline (Day 0) across the age groups (1,302.7 vs 10.6, respectively, for participants ≥ 18 years of age to < 65 years of age; and 899.8 vs 10.4 for participants ≥ 65 years of age), with no evidence of placebo response.

Figure 6: Study 301 (US/MX) – Neutralizing Antibody Responses



Abbreviations: CI = confidence interval; MN = microneutralization
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6 CLINICAL EFFICACY

Summary

- Phase 3 Study 301 (US/MX) demonstrated significant efficacy against COVID-19 variants
  - 90% efficacy in primary analysis (against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative adults).
  - 97% against strains antigenically similar to prototype strain.
  - 93% against Variants of Concern or Interest.
  - 100% against moderate or severe disease.
  - Consistent efficacy across subgroups of interest.

6.1 Phase 3 Study 301 (US/MX)

6.1.1 Study Design

6.1.1.1 Overall Design

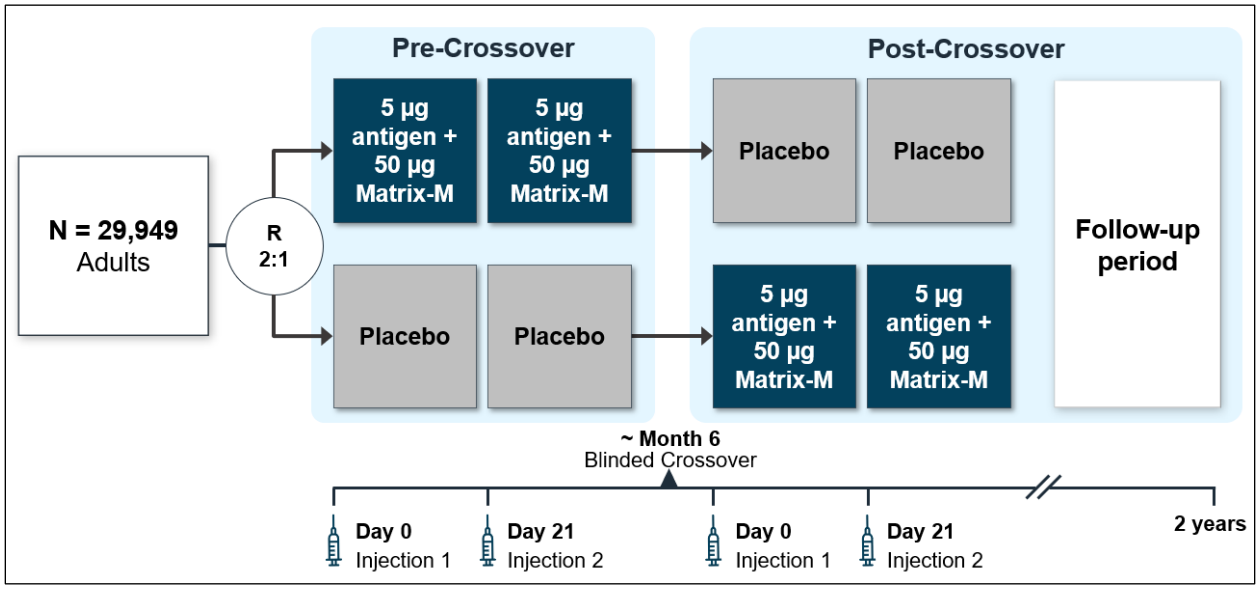
Study 301 (US/MX), also designated as the "PREVENT-19" study, is a randomized, observer -blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of NVX-CoV2373 in adults ≥ 18 years of age. Participants were stratified by age group prior to randomization, either 18 to 64 years or ≥ 65 years. At least 25% of the study population was intended to be in the ≥ 65 years age group. Most study participants were expected to be enrolled in the US.

Priority was given to enrolling individuals at high-risk for COVID-19 (in accordance with known data) by virtue of Black/African American or American Indian/Native American race, Hispanic or Latino ethnicity, comorbid conditions (eg, obesity [body mass index (BMI) > 30 kg/m^2]), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2) and life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [eg, factory or meat packing plants, essential retail workers, etc.]). Consideration was given to the enrollment of participants for whom vaccines that had previously received EUA were not, or not anticipated to be, recommended or available during the early months of this trial.

The study consisted of a screening period (up to 30 days prior to Day 0); initial vaccination days (Days 0 and 21 [+ 7 days]); and outpatient study visits on Days 0, 21, and 35 in the initial set of vaccinations. Following collection of sufficient safety data to support application for EUA, participants were administered two injections of the alternate study material 21 days apart (blinded crossover period). That is, initial recipients of placebo received NVX-CoV2373 and initial recipients of NVX-CoV2373 received placebo on Crossover Days 0 and 21 (+ 7 days).

Subsequent visits at Months 12 and 24 were performed to assess the durability of immune response, taking into account when participants received active vaccine (initial or crossover). An end of study visit was to be recorded for all study participants at approximately 24 months (± 30 days) after their initial set of vaccinations, or at their last visit on study (Figure 7).

Figure 7: Study Design for Study 301 (US/MX)



Abbreviations: R = randomization.

6.1.1.2 Enrollment Criteria

Key enrollment criteria for Study 301 (US/MX) are provided below; a complete list of the inclusion/exclusion criteria for the study is provided in Appendix 11.1.

Key Inclusion Criteria:

- Adults ≥ 18 years of age at screening who, by virtue of age, race, ethnicity or life circumstances, are considered at substantial risk of exposure to and infection with SARS-CoV-2.
- Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through 3 months after the last vaccination OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through 3 months after the last vaccination.
- Is medically stable.

Key Exclusion Criteria:

- Unstable acute or chronic illness.
- History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19.
- Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or ongoing therapy that causes clinically significant immunosuppression.
- Chronic administration of immunosuppressant or systemic glucocorticoids causing clinically significant immunocompromise within 90 days prior to first study vaccination and/or third (booster) vaccination.
- Received immunoglobulin or blood-derived products within 90 days prior to first study vaccination.

6.1.1.3 Statistical Analyses

6.1.1.3.1 Efficacy Endpoints

The primary and key secondary efficacy endpoints were defined as follows:

- **Primary Endpoint:** First occurrence of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset ≥ 7 days after second dose in serologically negative participants at baseline.
- **Key Secondary Endpoint:** First occurrence of PCR-confirmed symptomatic mild, moderate, or severe COVID-19, as defined in primary endpoint, shown by gene sequencing to represent a variant not considered as a variant of concern or variant of interest.
- **Secondary Endpoint:** First occurrence of PCR-confirmed moderate or severe COVID-19, as defined in primary endpoint.

The endpoint definitions for COVID-19 severity are summarized in Table 3.

Table 3: Endpoint Definitions for COVID-19 Severity

Severity	Endpoint Definition (≥ 1 of the following)
Mild	• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 additional COVID-19 symptoms: o New onset or worsening of shortness of breath or difficulty breathing compared to baseline. o New onset fatigue. o New generalized muscle or body aches. o New onset headache. o New loss of taste or smell. o Acute onset of sore throat, congestion, or runny nose o New onset nausea, vomiting, or diarrhea.
Moderate	• High fever (≥ 38.4°C) for at least 3 days (regardless of use of anti-pyretic medications, need not be contiguous days). • Any evidence of significant lower respiratory tract infection (LRTI) o Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline). o Tachypnea: 24 to 29 breaths per minute at rest. o SpO_2: 94% to 95% on room air. o Abnormal chest X-ray or chest CT consistent with pneumonia or LRTI. • Adventitious sounds on lung auscultation (eg, crackles/rales, wheeze, rhonchi, pleural rub, stridor).
Severe	• Tachypnea (≥ 30 breaths per minute at rest) • Resting heart rate ≥ 125 beats per minute • $SpO_2 \leq 93\%$ on room air or $PaO_2/FiO_2 < 300$ mmHg • High flow oxygen (O_2) therapy or NIV/NIPPV (eg, CPAP or BiPAP) • Mechanical ventilation or ECMO • One or more organ system dysfunction or failure o Acute respiratory failure, including ARDS. o Acute renal failure. o Acute hepatic failure. o Acute right or left failure. o Septic or cardiogenic shock (with shock defined as SBP < 90 mmHg or DBP < 60 mmHg). o Acute stroke (ischemic or hemorrhagic). o Acute thrombotic event: AMI, DVT, PE. o Requirement for vasopressors, systemic corticosteroids, or hemodialysis • Admission to an ICU • Death

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bilevel positive airway pressure; COVID-19 = coronavirus disease 2019; CPAP = continuous positive airway pressure; CT = computerized tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; NIPPV = non-invasive positive pressure ventilation; NIV = non-invasive ventilation; PaO_2 = partial pressure of oxygen; PE = pulmonary embolism; SBP = systolic blood pressure; SpO_2 = oxygen saturation.

6.1.1.3.2 Sample Size and Power

The sample size for the original study design was driven by the total number of cases expected to achieve statistical significance for the primary efficacy endpoint; a total of up to approximately 30,000 participants ≥ 18 years of age would be enrolled to provide a target of 144 symptomatic COVID-19 illness PCR-confirmed SARS-CoV-2 infections. With the change of the study design to perform a single efficacy analysis for the initial placebo-controlled phase at the implementation of the blinded crossover, the powers to reject the null hypothesis of VE lower bound of 95% CI ≤ 30% and achieving the point estimate of VE ≥ 50% simultaneously for the primary endpoint were re-estimated (through simulations). For assumed vaccine efficacy of 80%, the powers to reject the null hypothesis are presented in Table 4 for various numbers of endpoint events.

Table 4: Powers to Reject the Null Hypothesis

Number of Endpoint Events	Power
20	81%
25	85%
30	94%
35	95%
40	98%
45	98%
50	99%

6.1.1.3.3 Data Sets Analyzed

The data set presented in this document for the efficacy analysis in Study 301 (US/MX) was the PP-EFF Analysis Set, which included all participants who received the full prescribed regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (ie, participant was censored at the time of the protocol deviation) and were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR positivity. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. Although the study enrolled participants regardless of SARS-CoV-2 serologic status at the time of initial vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or anti-NP serology, were excluded from the PP-EFF population. PP-EFF was the primary set for all efficacy endpoints.

6.1.1.3.4 Efficacy Analysis

The primary efficacy endpoint is the first episode of PCR-positive nasal swab and symptomatic mild, moderate, or severe COVID-19 symptoms starting 7 days after the second vaccination in the initial vaccination period. VE was calculated in the initial vaccination period only. In order to be considered for EUA by the FDA, a vaccine must show superiority where there is a minimum

VE of 50% and a lower bound of two-sided alpha adjusted confidence bound of at least 30%. Based upon the number of primary efficacy endpoints planned for analysis, a lower bound of more than 30% corresponds with a vaccine efficacy point estimate of at least 50%.

The null and alternative hypotheses in this case were defined as:

- H_0:VE ≤ 30% (Relative risk [RR] ≥ 0.70)
- H_1:VE > 30% (RR < 0.70)

The primary analysis controlled for age cohort and was conducted with data collected up to the blinded crossover. The participant's follow-up time was censored at the time of crossover and other events.

6.1.1.4 Adjudication

For Study 301 (US/MX), potentially severe cases of symptomatic PCR-positive COVID-19 were reviewed by an external Independent Endpoint Review Committee (ERC).

6.1.1.5 Data and Safety Monitoring Board Oversight

An independent DSMB was chartered to periodically review study data, including unblinded study data if/when needed. In addition to reviewing safety data (see Section 7.1.2 for additional details), the DSMB reviewed formal interim analyses of efficacy and futility to make recommendations with regard to the continuation of the trial.

6.1.2 Demographics, Participant Disposition, and Baseline Characteristics

6.1.2.1 Demographics

Demographics and baseline characteristics of participants in the PP-EFF Analysis Set were well balanced between the NVX-CoV2373 and placebo groups as of the 27 September 2021 data cutoff date (data extraction date of 17 February 2022) (Table 5). Median age was 47.0 years, with all participants ranging in age from 18 to 95 years. Approximately 11.7% of participants were ≥ 65 years of age; while this was only about half of the projected target of at least 25%, the difference is attributable to availability and recommendation for use of EUA vaccines for older age groups in the US during the enrollment period. Approximately half the participants were male (51.5%), while the majority (75.9%) were White, not of Hispanic or Latino origin (78.3%), and located in the US (94.1%). Black or African Americans (11.0%), American Indians or Alaska Natives (6.2%), and Asians (4.4%) were well represented compared to the US population [23]. Approximately, a third of participants were obese (37.0%).

Demographics and baseline characteristics for participants included in the Safety Analysis Set, which was utilized for safety data displays presented in Section 7 (Clinical Safety) within the document, are summarized in Table 19 in Appendix 11.2.

Table 5: Study 301 (US/MX) - Demographics and Baseline Characteristics (Data Cutoff: 27 September 2021; PP-EFF Analysis Set)

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
Min, max	18, 95	18, 90	18, 95
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 or Latino	13526 (78.3)	6572 (78.4)	20098 (78.3)
Hispanic or 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)

Abbreviations: BMI = body mass index; eCRF = electronic case report form; max = maximum; min = minimum; NP = nucleocapsid protein; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation; US = United States.

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 American Indians enrolled at sites in the US.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.2.2 Disposition

In total, 31,592 participants were screened, 29,945 (94.8%) participants were randomized and 1,641 participants were screen failed (5.2%) (Table 6). The most frequent (incidence > 1.0%) reason for screen failure was failure to meet inclusion/exclusion criteria.

Table 6: Study 301 (US/MX) - Participant Screening and Enrollment (All Screened Participants)

Parameter	Participants
Total number of participants, n (%)	
Screened	31,592 (100.00)
Screen failed	1,641 (5.2)
Randomized	29,945 (94.8)
Primary reason for screen failure, n (%)	
Failure to meet inclusion/exclusion criteria	1,378 (4.4)
Withdrawal by participant	193 (0.6)
Other	43 (0.1)
Lost to follow-up	25 (< 0.1)
Failure to meet randomization criteria	1 (< 0.1)
Adverse event	1 (< 0.01)

Denominator is the number of participants screened.
Abbreviations: CI = confidence interval; MN = microneutralization
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Of the 29,945 participants randomized, 19,963 were in the NVX-CoV2373 group and 9,982 were in the placebo group (Table 7). A total of 4,599 (15.5%) participants discontinued the study during the original blinded placebo-controlled vaccination period, with 2,407 (12.2%) in the NVX-CoV2373 group and 2,192 (22.2%) in the placebo group. The most frequent (incidence > 1.0%) reasons for study discontinuation were withdrawal by participant (10.7%) and lost to follow-up (4.2%), which occurred in 1,563 and 741 (7.9% and 3.8%, respectively) participants, in the NVX-CoV2373 group and 1,604 and 501 (16.3% and 5.1%, respectively) participants in the placebo group. A total of 24 (< 0.1%) participants discontinued the study due to an AE, with 18 (< 0.1%) in the NVX-CoV2373 group and 6 (< 0.1%) in the placebo group.

For the blinded crossover vaccination period, 15,319 (77.7%) participants in the NVX-CoV2373 group crossed over to receive placebo and 6,395 (64.8%) participants in the placebo group crossed over to receive NVX-CoV2373, with nearly 99% of participants receiving both doses of trial vaccine. A total of 860 (2.9%) participants discontinued the study during the blinded crossover vaccination period, with 666 (3.4%) participants in the NVX-CoV2373 group and 194 (2.0%) in the placebo group. A total of 231 (0.8%) participants discontinued the study after Dose 3 but on or before the Dose 4 administration date and 629 (2.1%) participants discontinued the study after Dose 4. The most frequent (incidence > 1%) reason for study discontinuation was withdrawal by participant (1.8%).

During the initial vaccination series, a higher proportion of placebo participants (12.9%) than NVX-CoV2373 participants (3.5%) chose to receive an EUA vaccine. In the blinded crossover period, the proportion of participants who reported receiving an EUA vaccine was similar between NVX-CoV2373 and placebo participants (2.4% and 3.5%, respectively).

Table 7: Study 301 (US/MX) - Participant Disposition (All Randomized Participants)

Parameter	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
Randomized	19963	9982	29945
Treated	19714 (100)	9868 (100)	29582 (100)
Blinded, placebo-controlled follow-up period			
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 placebo-controlled vaccination period	2407 (12.2)	2192 (22.2)	4599 (15.5)
Reason for discontinuation			
Withdrawal by participant	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)
Blinded crossover period			
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)	21430 (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 vaccination period	666 (3.4)	194 (2.0)	860 (2.9)
Discontinued after dose 3 but before dose 4	175 (0.9)	56 (0.6)	231 (0.8)
Reason for discontinuation			
Withdrawal by participant	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)

Abbreviations: NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

Note: Denominators are based on the number of treated participants.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.3 Epidemiological Setting

A number of Variants of Concern or Interest circulated during the study, with the Alpha variant being predominant. Sequence data were available for 75 of the endpoint cases in adult participants; 61 of these cases, or about 80%, were due to Variants of Concern or Variants of Interest, with the Alpha variant being the most common (Table 8).

Table 8: Study 301 (US/MX) –Variants of Concern or Interest Identified During the Study

Variant	Number and % of Cases* (n = 75)
Alpha[1]	40 (53%)
Iota[2]	8 (11%)
Epsilon[1]	5 (7%)
Gamma[1]	3 (4%)
Beta[1]	2 (3%)
Delta[2]	1 (1%)
Kappa[2]	1 (1%)
Zeta[2]	1 (1%)
Total	61 (81%)

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.
CDC variant classification as of 25 May 2021
n = number of cases with sequence data available.
1. Variants of Concern
2. Variants of Interest
* Out of 96 cases in the analysis, 75 (78%) had sequence data available

6.1.4 Study 301 (US/MX) Results

6.1.4.1 Primary Analysis Results

For the analysis of the primary endpoint (using data cutoff date of 27 September 2021), there was 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 this analysis (Table 9). Of these cases, 17 (0.098%) were in the NVX-CoV2373 group and 79 (0.942%) were in the placebo group. All 17 cases in the NVX-CoV2373 group were mild in severity, while 13 cases in the placebo group were moderate (9 cases) or severe (4 cases). The resultant VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative adult participants was 90.41% (95% CI: 83.81, 94.32), with a p-value of < 0.001 confirming the lower bound of the two-sided 95% CI > 30% and meeting the prespecified study success criterion.

The Kaplan-Meier curve shows that cases began to diverge between the placebo and vaccine arms at around the time of the second dose at Day 21, and that there were few cases in the vaccine arm through Day 98 (Figure 8).

Table 9: Study 301 (US/MX) - Vaccine Efficacy against PCR-Confirmed Mild, Moderate, or Severe COVID-19 Starting 7 Days After Dose 2 in Serologically Negative Adults (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 17272	Placebo N = 8385
Participants with no occurrence of event[1], n (%)	17255 (99.902)	8306 (99.058)
Participants with occurrence of event[2], n (%)	17 (0.098)	79 (0.942)
Severity of first occurrence, n (%)		
Mild	17 (0.098)	66 (0.787)
Moderate	0	9 (0.107)
Severe	0	4 (0.048)
Median surveillance time (days)	63.0	57.0
Log-linear model[3,4]		
Mean disease incidence rate per year in 1000 people	4.34	45.25
95% CI	2.33, 8.08	29.86, 68.56
Relative risk[3 4]	0.10	
95% CI	0.06, 0.16	
Vaccine efficacy (%)	90.41	
95% CI	83.81, 94.32	
p-value[5]	< 0.0001	

CI = Confidence Interval; SD = Standard Deviation.

Event = First occurrence of PCR-confirmed Mild, Moderate or Severe COVID-19 Disease with Onset from 7 days after Second Injection within the Surveillance period.

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 receive both doses of study material in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo group (SARS-CoV-2 Matrix-M/placebo) with first occurrence of event with onset during a surveillance period from 7 days after Second Injection up to censor date as defined below.

Surveillance time is defined as the difference between the date at end of surveillance period (onset of first occurrence of event/censoring) and date at start of surveillance period (7 days after the Second Injection)+ 1. Participants are censored at the earliest of (i) cut-off date (2021-09-27), (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. Participants PCR-Positive and who did not meet mild, moderate or severe COVID-19 disease criteria were censored at date of the PCR-Positive.

1 Includes participants with PCR-Positive who did not meet mild, moderate or severe COVID-19 disease criteria. Event is defined as first occurrence of PCR-Confirmed Mild, Moderate or Severe COVID-19 Disease with Onset from 7 Days after the Second Injection within the Surveillance Period.

2 Denominator is the number of participants in the Per-Protocol Efficacy Analysis Set within each treatment group and total. Surveillance time is defined as the difference between the date at end of surveillance period (onset of first occurrence of event, or censoring) and date at start of surveillance period (7 days after the Second Injection) + 1. Participants are censored at the earliest of (i) cut-off date (2021-09-27), (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.

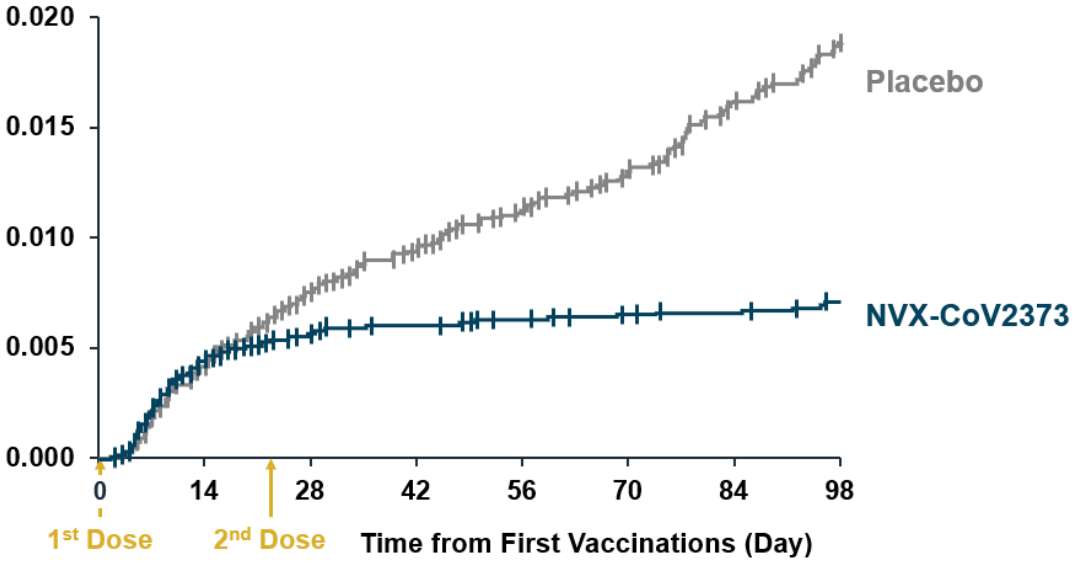
3 Modified Poisson regression with logarithmic link function and treatment group and age strata as fixed effects and robust error variance [24].

4 In case when there are zero cases in either groups 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.

5 This p-value corresponds to a one-sided hypothesis test with significance level 0.025. If the VE p-value < 0.025, then reject H0: VE <= 30%.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Figure 8: Study 301 (US/MX): Kaplan-Meier Curve Efficacy and Durability of Two-Dose Regimen in Adults



N at risk

NVX-CoV2373	19,714	19,483	19,000	18,311	17,568	16,863	13,015	7,925
Placebo	9,868	9,720	9,410	8,773	8,082	7,482	5,654	3,435

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.4.2 Efficacy Against Moderate or Severe COVID 19

There were 13 cases of PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination accrued for this analysis, with 0 in the NVX-CoV2373 group and 13 (0.155%) in the placebo group (Table 10). The resultant VE of NVX-CoV2373 to prevent symptomatic moderate or severe COVID-19 in baseline seronegative (to SARS-CoV-2) adult participants was 100.00% (95% CI: 85.41, 100.00).

Table 10: Study 301 (US/MX) - Vaccine Efficacy against PCR-Confirmed Moderate or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adult Participants (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 17272	Placebo N = 8385
Participants with no occurrence of event[1,2], n (%)	17272 (100.0)	8372 (99.845)
Participants with occurrence of event[2], n (%)	0 (0.000)	13 (0.155)
Severity of first occurrence[2], n (%)		
Moderate	0 (0.000)	9 (0.107)
Severe	0 (0.000)	4 (0.048)
Median surveillance time (days)	63.0	57.0
Log linear model[3,4]		
Mean disease incidence rate per year in 1000 people	0.00	9.79
95% CI	0.00, 1.24	5.22, 16.75
Relative risk[3,4]	0.00	
95% CI	0.00, 0.15	
Vaccine efficacy (%)	100.00	
95% CI	85.41, 100.00	
p-value[5]	<0.0001	

CI = Confidence Interval; SD = Standard Deviation.

Event = First occurrence of PCR-Confirmed Moderate or Severe COVID-19 Disease with Onset from 7 Days after the Second Injection within the Surveillance Period.

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 receive both doses of study material in the pre-crossover period. RR is ratio of incidence rates of active group relative to the placebo group (SARS-CoV-2 Matrix-M/placebo) with first occurrence of event with onset during a surveillance period from 7 days after Second Injection up to censor date as defined below.

Surveillance time is defined as the difference between the date at end of surveillance period (onset of first occurrence of event/ censoring) and date at start of surveillance period (7 days after the Second Injection) + 1. Participants are censored at the earliest of (i) cut-off date (2021-09-27), (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. Participants PCR-Positive and who did not meet Moderate or Severe COVID-19 disease criteria were censored at date of the PCR-Positive.

1 Includes participants with PCR-Positive who did not meet moderate or severe COVID-19 disease criteria.

2 Denominator is the number of participants in the Per-Protocol Efficacy Analysis Set within each treatment group and total. Surveillance time is defined as the difference between the date at end of surveillance period (onset of first occurrence of event, or censoring) and date at start of surveillance period (7 days after the Second Injection) + 1. Participants are censored at the earliest of (i) cut-off date (2021-09-27), (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.

3 Modified Poisson regression with logarithmic link function and treatment group and age strata as fixed effects and robust error variance [24].

4 In case when there are zero cases in either groups 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.

5 This p-value corresponds to a one sided hypothesis test with significance level 0.025. If the VE p-value < 0.025, then reject H0: VE ≤ 0%.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.4.3 Efficacy Against COVID-19 Due to a SARS-CoV-2 Variant Not Considered a Variant of Concern or Interest

Through the observation period covered by this analysis, the circulation of variant strains evolved in the US such that the predominantly circulating strains were Variants of Concern or Interest according to CDC SARS-CoV-2 Variant Classifications and Definitions [25]. Since NVX-CoV2373 contains the recombinant S protein produced from the prototype (Wuhan) genome, VE against "prototype-like" or "matched" strains (ie, those not considered as a variant of concern or interest) was identified as the key secondary endpoint of the study.

Of the 96 primary endpoint cases in the PP-EFF Analysis Set, viral genetic sequences were available for 75 participants. Fourteen of these cases (1 [< 0.1%] in the NVX-CoV2373 group and 13 [0.2%] in the placebo group) were prototype-like and did not contain any of the mutations that would identify them as a Variant of Concern or Interest, including 3 cases that were moderate or severe (Table 11). The resultant VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant not considered as a Variant of Concern or Interest in serologically negative adult participants was 96.57% (95% CI: 73.78, 99.55; $p < 0.0018$).

Table 11: Study 301 (US/MX) – Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 Due to a SARS-CoV-2 Variant Not Considered as a Variant of Concern or Interest with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adults (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 17272	Placebo N = 8385
Participants with no occurrence of event[1], n (%)	17271 (100.0)	8372 (99.845)
Participants with occurrence of event[2], n (%)	1 (0.006)	13 (0.155)
Severity of first occurrence, n (%)		
Mild	1 (0.006)	10 (0.119)
Moderate	0 (0.0)	2 (0.024)
Severe	0 (0.0)	1 (0.012)
Median surveillance time[3] (days)	63.0	57.0
Log-linear model using modified Poisson regression[4]		
Mean disease incidence rate per year in 1000 people	0.27	7.94
95% CI	0.03, 2.18	2.81, 22.41
Relative risk	0.03	
95% CI	0.00, 0.26	
Vaccine efficacy (%)	96.57	
95% CI	73.78, 99.55	
p-value[5]	0.0018	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PCR = polymerase chain reaction; PP-EFF = Per-Protocol Efficacy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein vaccine; SIG = SARS-CoV-2 Interagency Group; VE = vaccine efficacy; VOC = Variant of Concern; VOI = Variant of Interest.

1. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria and not considered a VOC or VOI.
2. Event = first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant not considered as a VOC or VOI with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
3. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of event/censoring) and date at start of surveillance period (7 days after the Second Injection) + 1.
4. Modified Poisson regression with logarithmic link function, treatment group and strata as fixed effects and robust error variance [24].
5. This p-value corresponded to a one-sided hypothesis test with significance level 0.025. If the VE p-value < 0.025, then reject H0: VE ≤ 30%.

Note: VOC/VOI were established by SIG and CDC for SARS-CoV-2 Variant Classifications and Definitions [25].
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.4.4 Efficacy Against COVID-19 Due to a SARS-CoV-2 Variant Considered a Variant of Concern or Interest

In the PP-EFF Analysis Set, 61 cases (8 [< 0.1%] in the NVX-CoV2373 group and 53 [0.6%] in the placebo group) had mutations that would identify them as a Variant of Concern or Interest (Table 12). In the NVX-CoV2373 group, all 8 cases were mild in severity; whereas, in the placebo group, 9 of 53 cases were moderate or severe. The resultant VE of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant

considered a Variant of Concern or Interest in baseline seronegative adult participants in a post-hoc analysis was 93.26% (95% CI: 85.84, 96.80).

Table 12: Study 301 (US/MX) – Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 Due to a SARS-CoV-2 Variant Considered as a Variant of Concern or Interest with Onset from at Least 7 Days after Second Vaccination in Serologically Negative Adults (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 17272	Placebo N = 8385
Participants with no occurrence of event[1], n (%)	17264 (100.0)	8332 (99.368)
Participants with occurrence of event[2], n (%)	8 (0.046)	53 (0.632)
Severity of first occurrence, n (%)		
Mild	8 (0.046)	44 (0.525)
Moderate	0 (0.0)	7 (0.083)
Severe	0 (0.0)	2 (0.024)
Median surveillance time[3] (days)	63.0	57.0
Log-linear model using modified Poisson regression[4]		
Mean disease incidence rate per year in 1000 people	1.51	22.34
95% CI	0.53, 4.25	11.17, 44.68
Relative risk	0.07	
95% CI	0.03, 0.14	
Vaccine efficacy (%)	93.26	
95% CI	85.84, 96.80	

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PCR = polymerase chain reaction; PP-EFF = Per-Protocol Efficacy; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein vaccine; VE = vaccine efficacy.

1. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria and not considered a variant of concern or interest.
2. Event = first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 due to a Variants of Concern or Interest with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
3. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of event/ censoring) and date at start of surveillance period (7 days after the Second Injection) + 1.
4. Modified Poisson regression with logarithmic link function, treatment group and strata as fixed effects and robust error variance [24].

Note: Variants of concern or interest were established by SIG and CDC for SARS-CoV-2 Variant Classifications and Definitions CDC [25].

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

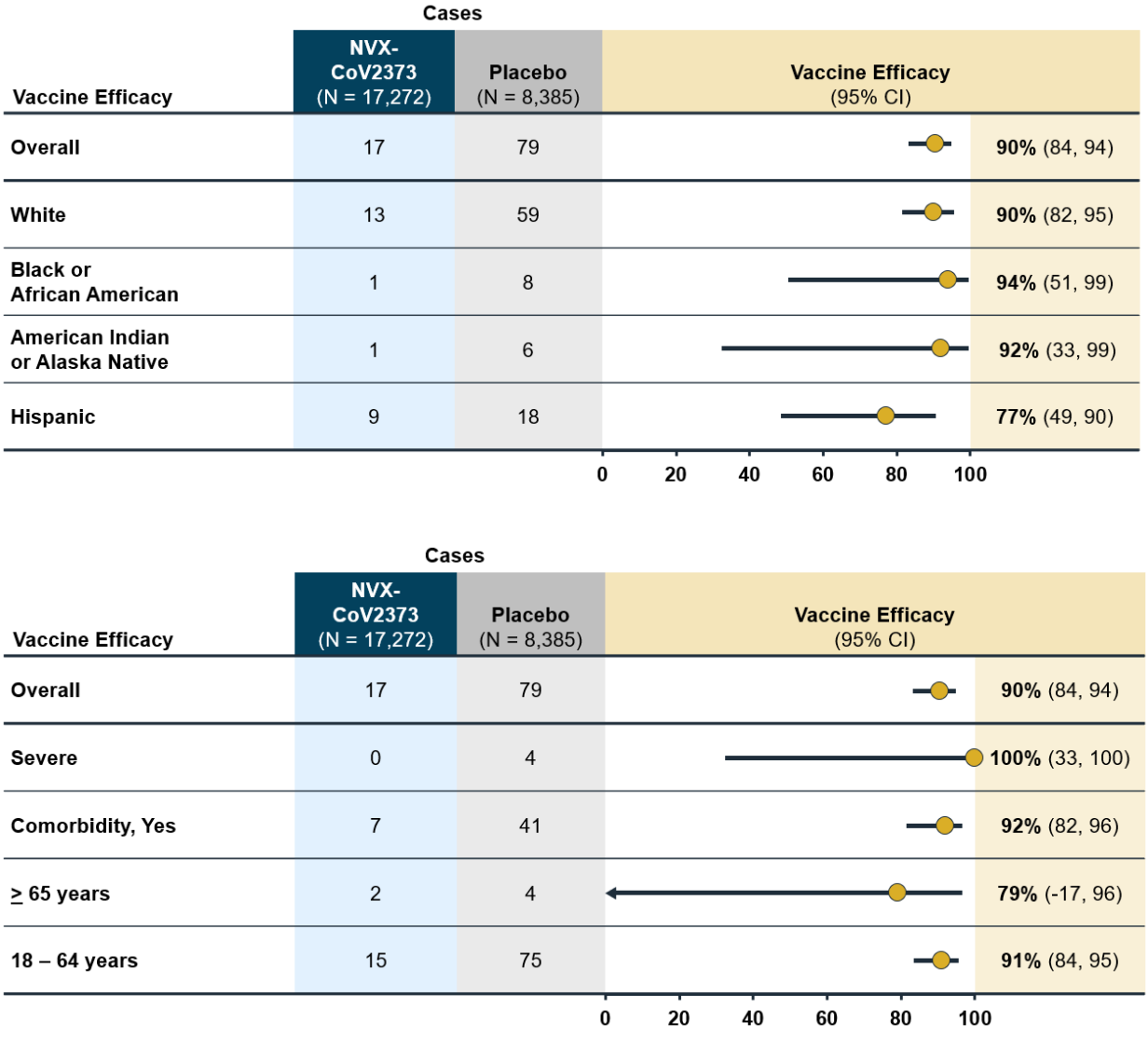
6.1.4.5 Subgroup Analysis

Subgroup analyses based on key demographic and baseline characteristics are shown in Figure 9.

The VEs across subgroups were generally similar to the results for the primary analysis. Regarding VE within subgroups by race, the vaccine provided a consistently high level of protection across all groups. When examined by ethnicity, the VE for Hispanic or Latino participants was somewhat lower than that seen for the overall study population, but with wide confidence intervals. In order to evaluate this result in more detail, immune responses, immune

responses were examined as a potential contributing factor; however, the data indicated that IgG and neutralizing antibodies in Hispanic/Latino participants were actually slightly higher than those seen in non-Hispanic/Latino participants.

Figure 9: Study 301 (US/MX): Analyses for Overall Population and Key Subgroups for the Primary Efficacy Endpoint (PP-EFF Analysis Set)



Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

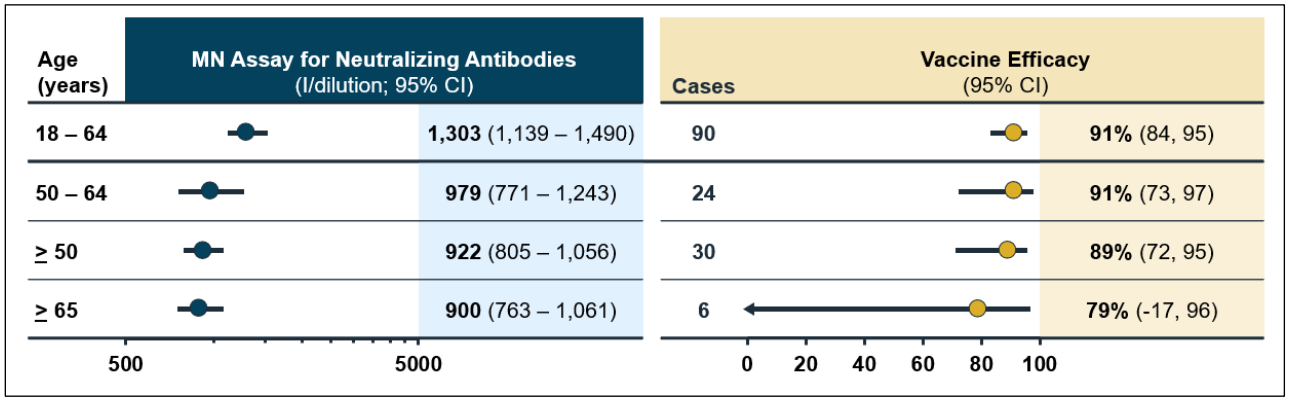
6.1.4.6 Immunogenicity and Efficacy by Age

The relationship between geometric mean neutralizing antibody titers, efficacy, and age in the analysis that was performed to evaluate all of the COVID-19 cases that occurred in the study before the crossover doses were given is shown in Figure 10. Adults of 18 to 64 years of age had a neutralizing antibody titer of 1,303, which was associated with approximately 91% VE. Within this group, there did not appear to be a decrease in efficacy associated with older age; efficacy

remained at 91% for the 50 to 64 years of age range, even though the antibody titer for those participants was somewhat lower than for the overall group, at 979.

The efficacy estimate for the group of all adults 50 or older was 89%, with a corresponding neutralizing antibody titer of 922. Finally, for participants 65 years of age or older, the antibody titer was 900 and the efficacy estimate was 79%, with a wide confidence interval, based on there being only 6 COVID-19 cases in this age group. Based on the similarity of the neutralizing antibody titers acorss the age groups, and the fact that the 95% confidence interval for the older adult efficacy estimate overlaps that for younger adults, the efficacy estimate in older adults is attributed to the relatively limited number of cases accrued. Supportive data for the efficacy of the vaccine in older adults are available from Study 302 (UK) (Figure 5; see reference to published paper provided in the figure footnote).

Figure 10: Study 301 (US/MX): Analysis of Immunogenicity and Efficacy by Age (PP-EFF Analysis Set)



Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

6.1.5 Efficacy Conclusions

The results from Study 301 (US/MX) show that NVX-CoV2373 exhibited a high level of efficacy for prevention of mild, moderate, and severe COVID-19. In addition, the vaccine provided complete protection from moderate and severe COVID-19, an endpoint with important public health implications. The vaccine also demonstrated a high level of efficacy for Variants of Concern or Interest that were responsible for approximately 80% of the cases during the study for which sequence data were available, and demonstrated high levels of efficacy across subgroups.

7 CLINICAL SAFETY

Summary

- NVX-CoV2373 safety data supports a positive benefit-risk profile, which includes a favorable reactogenicity profile.
- Safety was well-characterized, with exposure to NVX-CoV2373 in > 30,000 recipients pre-crossover and > 40,000 recipients including post crossover doses across all studies.
    - In Study 301 (US/MX), 19,729 participants received NVX-CoV2373 pre-crossover and > 26,000 participants including post crossover doses.
- From Study 301 (US/MX):
    - Local and systemic events were generally mild to moderate and of short duration.
    - Most AEs were of mild to moderate severity.
    - SAE rates were low in the NVX-CoV2373 group and comparable to placebo.

7.1 Safety Assessments

Safety assessments in the NVX-CoV2373 clinical studies included monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs, SAEs, MAAEs, vital sign measurements, and physical examinations.

Safety data were also reviewed by independent safety monitoring committees (SMC) for the individual studies, which were formed before the first participant was vaccinated. The SMCs reviewed study progress and participant, clinical, safety, and reactogenicity data for immediate concerns regarding observations during the study to allow the study to continue or to suggest modifications to the study design, as needed. The National Institute of Allergy and Infectious Diseases (NIAID) independent DSMB was charged with oversight of safety data in Study 301 (US/MX). No modifications to study conduct were recommended by the independent committees.

The Safety Analysis Set included all participants who received at least one dose of NVX-CoV2373 or 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.

7.1.1 Safety Follow-up Periods

In Study 301 (US/MX), the data cutoff date for the Safety Analysis Set was 27 September 2021 (data extraction date of 17 February 2022).

For the initial vaccination period (pre-crossover), median follow-up post Dose 2 was 2.5 months with 77.6% of participants in the NVX-CoV2373 group and 72.8% of participants in the placebo group being followed for at least 2 months post-Dose 2.

For the blinded crossover vaccination period (post-crossover), median follow-up post Dose 4 was 4.4 months with approximately 99% of participants being followed for at least 2 months post Dose 4.

The Study 301 (US/MX) Safety Analysis Set includes more than 8,000 PY of follow-up across both active and placebo groups: 5,511 in the NVX-CoV2373 group and 2,783 in the placebo group.

7.1.2 Data Safety Monitoring Board

A centralized DSMB was established in collaboration with the National Institutes of Health, NIAID, Biomedical Advanced Research and Development Authority, and Novavax. This group reviewed interim unblinded data regularly in the study and made recommendations with respect to safety and emerging efficacy. The NIAID DSMB assessed the effects of the study vaccine during the trial, provided monitoring, and gave advice to the Study 301 team leadership, the Oversight Group, and Protocol Safety Review Team (PSRT).

The DSMB periodically reviewed accumulating unblinded safety data by treatment group. Prior to each meeting, the ICON unblinded statistician provided the DSMB with data as described in the SAP. Reports are cumulative, generated from an up-to-date data file. Based on the reports, the DSMB determined whether to recommend that the study should be continued, modified, or stopped, including for safety reasons.

The DSMB could recommend any steps to ensure the safety of study participants and the integrity of the trial. Furthermore, the DSMB could recommend that the trial be terminated or that specific groups be withdrawn from the study, if any subgroup manifests serious or widespread side effects. During the reviews conducted, the DSMB did not identify any safety concerns that led to changes in study conduct.

7.2 Treatment Exposure

In Study 301 (US/MX), in the initial vaccination period (pre-crossover), 29,582 participants received at least one dose of trial vaccine with 19,735 in the NVX-CoV2373 group and 9,847 in the placebo group. Among these participants, 3,715 were ≥ 65 years old (2,480 NVX-CoV2373; 1,235 placebo). Approximately 96% of participants received both doses of trial vaccine.

In the blinded crossover vaccination period (post-crossover), 21,714 participants received at least one dose of the alternate trial vaccine with 15,298 crossed over to receive placebo and 6,416 crossed over to receive NVX-CoV2373. Of these participants, nearly 99% received both doses of trial vaccine.

7.3 Adverse Events

7.3.1 Solicited Adverse Events

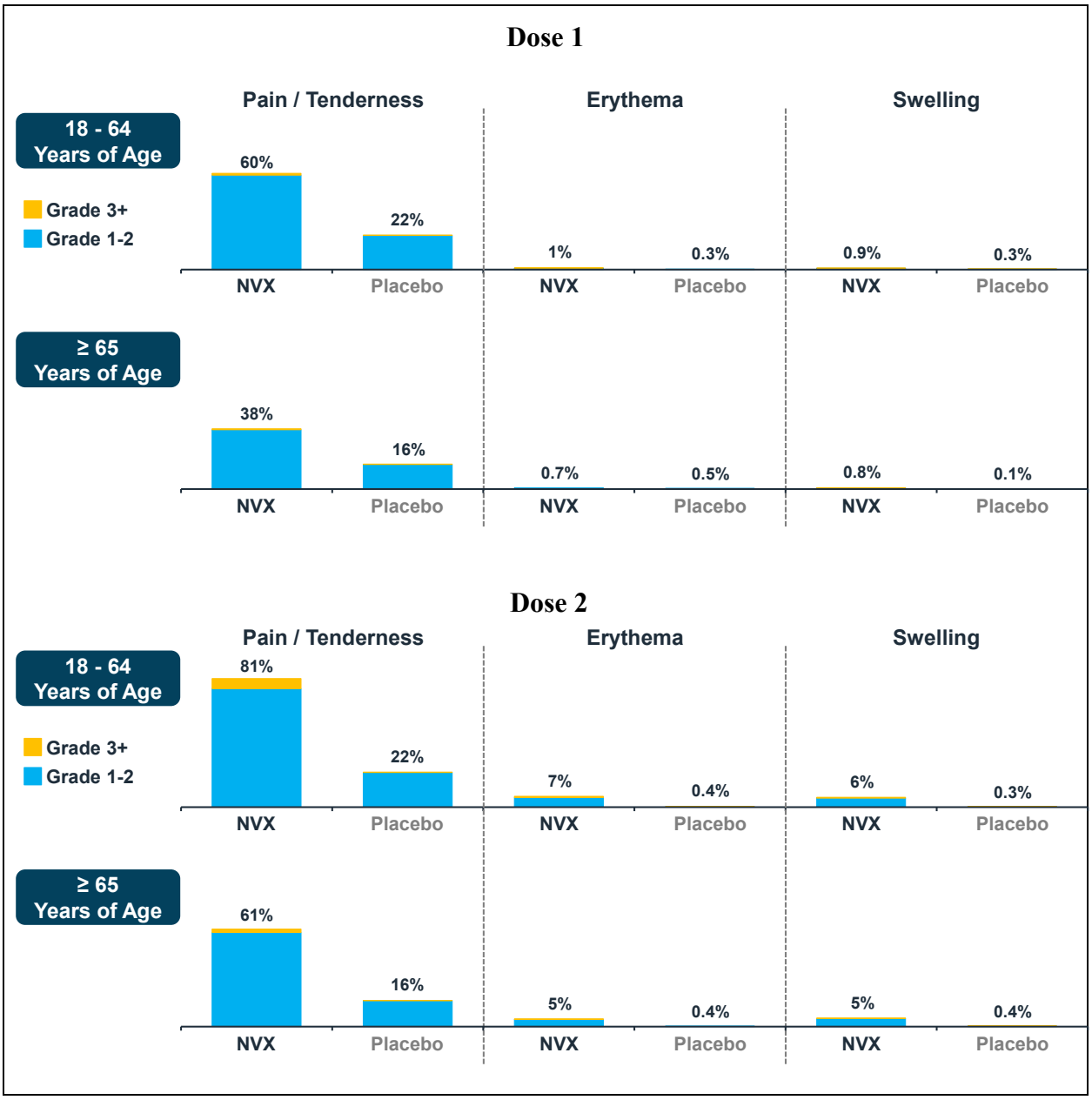
7.3.1.1 Solicited Local Adverse Events

Solicited local AEs were recorded by each participant in an e-diary from the start of each study vaccination until 7 days after each study vaccination during the pre-crossover period. Solicited local AEs consisted of pain/tenderness, erythema, and swelling at the injection site.

In Study 301 (US/MX), a greater proportion of participants in the NVX-CoV2373 group reported solicited local AEs following each vaccination compared to the placebo group (Table 20 in Appendix 11.2). In the NVX-CoV2373 group, the frequency and intensity of solicited local AEs increased after second vaccination relative to the first vaccination, but NVX-CoV2373 remained well tolerated. Most solicited local AEs reported following each vaccination were Grade 1 or Grade 2 (Figure 11). Frequencies of Grade 3 and higher events were relatively low (< 10%), but such events generally occurred more frequently in the NVX-CoV2373 group than in the placebo group. Grade 4 events were reported in few participants (< 1.0%) in either group and were primarily participant-reported events that were miscategorized through data entry error by the participants in their e-diary. The most frequent solicited local AE following each vaccination was pain/tenderness. The median duration of solicited local AEs was generally 2 days or fewer.

A comparison of age groups (18 to 64 and ≥ 65 years) shows that participants in the older age cohort reported a lower frequency and intensity of solicited local AEs than participants in the younger age cohort, which is an expected finding (Figure 11, Table 21, and Table 22 in Appendix 11.2).

Figure 11: Local Adverse Events Reported Within 7 Days of Either Vaccination in Adults (18 – 64 or ≥ 65 Years Old) in Study 301 (US/MX) (Ad Hoc Dataset)



Note: includes events reported Day 0 to Day 6 post-vaccination; Grades based on FDA guidance
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

7.3.1.2 Solicited Systemic Adverse Events

Solicited systemic AEs were recorded by each participant in an e-diary from the start of each study vaccination until 7 days after each study vaccination during the pre-crossover period. Solicited systemic AEs consisted of headache, fatigue/malaise, muscle pain, joint pain, fever, and nausea/vomiting.

Similar to solicited local AEs, there were higher frequencies of systemic AEs among NVX-CoV2373 recipients than among placebo recipients following each vaccination in Study 301 (US/MX) (Table 23 in Appendix 11.2). The frequency and intensity of solicited systemic AEs increased after second vaccination relative to the first vaccination in the NVX-CoV2373 group (Figure 12). Most events in the NVX-CoV2373 group were Grade 1 or Grade 2. Frequencies of Grade 3 events were relatively low (< 12%) but greater in the NVX-CoV2373 group than in the placebo group. Grade 4 events were reported in few participants (< 1.0%) in either group and were participant-reported events that mostly were acknowledged as data entry errors by participants in the e-diaries. The most frequent (incidence > 20.0% after each vaccination) solicited systemic AEs following each vaccination were fatigue/malaise, headache, and muscle pain. The median duration of solicited systemic AEs was generally 2 days or less.

As expected, a comparison of age groups (18 to 64 and ≥ 65 years) shows that participants in the older age cohort reported a lower frequency and intensity of solicited systemic AEs than participants in the younger age cohort (Figure 12, Table 24, and Table 25 in Appendix 11.2).

Figure 12: Systemic Adverse Events Reported Within 7 Days of Either Vaccination by Age (18 – 64 or ≥ 65 years Old) in Study 301 (US/MX) (Ad Hoc Dataset)

Note: includes events reported Day 0 to Day 6 post-vaccination; Grades based on FDA guidance
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

7.3.2 Unsolicited Adverse Events

Unsolicited AEs were recorded by the investigator or designee from the start of first vaccination through 28 days after second vaccination (eg, Day 49) during the pre-crossover period.

In Study 301, the overall frequency of non-serious unsolicited AEs was similar between the NVX-CoV2373 group (11.6%) and the placebo group (11.2%) (Table 13). The frequencies of MAAEs, severe AEs, SAEs, and PIMMCs were relatively balanced between groups.

During the pre-crossover period, there were 11 deaths (< 0.1%) in the NVX-CoV2373 group and 5 deaths (< 0.1%) in the placebo group. During the post-crossover period, there were 6 deaths (< 0.1%) and 10 deaths (< 0.1%), respectively.

Table 13: Summary of Unsolicited Adverse Events in Adults in Study 301 (US/MX) (Ad Hoc Dataset)

Participants reporting at least one	NVX-CoV2373 n/N (%)	Placebo n/N (%)
Unsolicited adverse event[1]		
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)
Medically attended adverse event		
Pre-crossover period	1144/19735 (5.8)	558/9847 (5.7)
Post-crossover period	299/6416 (4.7)	610/15298 (4.0)
SAE		
Pre-crossover period	199/19735 (1.0)	108/9847 (1.1)
Post-crossover period	88/6416 (1.4)	178/15298 (1.2)
AESI (PIMMCs)[2]		
Pre-crossover period	35/19735 (0.2)	19/9847 (0.2)
Post-crossover period	11/6416 (0.2)	15/15298 (< 0.1)
AESI (related to COVID-19)		
Pre-crossover period	7/19735 (< 0.1)	6/9847 (< 0.1)
Post-crossover period	3/6416 (< 0.1)	3/15298 (< 0.1)
Deaths		
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		
Pre-crossover period	67/19735 (0.3)	22/9847 (0.2)
Post-crossover period	4/6416 (< 0.1)	13/15298 (< 0.1)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PIMMC = potential immune-mediated medical condition; SAE = serious adverse event; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

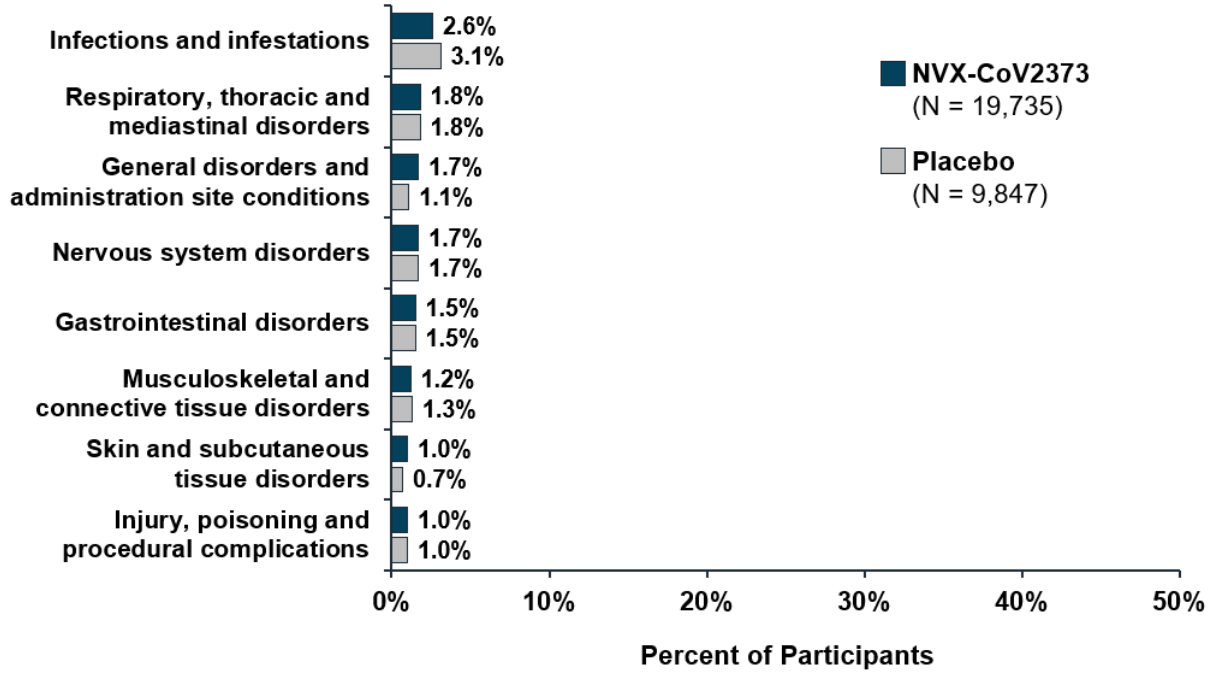
[1] Reported within 28 days of any dose.

[2] Based on investigator reporting and protocol-defined criteria.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Figure 13 shows the rates of unsolicited AEs in adults from Study 301 (US/MX) by SOC, the most common of which was infections and infestations (2.6% vs 3.1% for NVX-CoV2373 and placebo, respectively), followed by respiratory, thoracic and mediastinal disorders (1.8% vs 1.8%, respectively), nervous system disorders (1.7% vs 1.7%, respectively) and general disorders and administration site conditions (1.7% vs 1.1%, respectively). Headache was the only unsolicited AE in the pre-crossover period that was reported in 1% or more participants in either the NVX-CoV2373 or placebo groups, with the same frequency in both treatment groups (1.1%).

Figure 13: Rates of Unsolicited Adverse Events (≥ 1% of Adult Participants) from Day 0 to Day 49 (28-Days Post-Dose 2) by System Organ Class in Study 301 (US/MX) (Ad Hoc Dataset)



Note: includes events reported through Day 49
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

7.3.3 Potential Immune-Mediated Medical Conditions

PIMMCs are AESIs that include autoimmune diseases and other inflammatory disorders of interest that may or may not have an autoimmune etiology. PIMMCs are considered a theoretical risk for all vaccines containing an adjuvant.

Table 14 summarizes the PIMMCs in Study 301 (US/MX) based on investigator reporting and protocol defined criteria from after the start of first vaccination through the data cutoff date.

For the pre-crossover period, the most frequent PIMMCs (IR ≥ 0.05 e/100 PY) by preferred term in the NVX-CoV2373 group were Bell's palsy, neuropathy peripheral, seizure, and uveitis, all of which had an IR of 0.1. In the placebo group, events with an IR ≥ 0.05 e/100 PY were neuropathy peripheral, seizure, and uveitis, all of which had an IR of 0.1.

During the post-crossover period, the only PIMMC by preferred term that was reported by more than one participant in the NVX-CoV2373 group was rheumatoid arthritis, with two participants each reporting a single event.

Table 14: Potential Immune-Mediated Medical Conditions (PIMMCs) by Preferred Term for System Organ Classes with > 1 Participant Reporting an Event Based on Investigator Reporting and Protocol Defined Criteria in Study 301 (US/MX) (Safety Analysis Set)

	Pre-Crossover Period						Post-Crossover Period					
	NVX-CoV2373 N = 19735			Placebo N = 9847			NVX-CoV2373 N = 6416			Placebo N = 15298		
System Organ Class/ Preferred Term	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**
Any System Organ Class	**36**	**35 (0.2)**	**0.6**	**20**	**19 (0.2)**	**0.7**	**14**	**11 (0.2)**	**0.5**	**15**	**15 (< 0.1)**	**0.2**
Blood and lymphatic system disorders	**2**	**2 (< 0.1)**	**0.0**	**1**	**1 (< 0.1)**	**0.0**	**0**	**0**	**0.0**	**2**	**2 (< 0.1)**	**0.0**
Thrombocytopenia	2	2 (< 0.1)	0.0	1	1 (< 0.1)	0.0	0	0	0.0	2	2 (< 0.1)	0.0
Endocrine disorders	**3**	**3 (< 0.1)**	**0.1**	**1**	**1 (< 0.1)**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Autoimmune thyroiditis	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Basedow's disease	2	2 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Eye disorders	**4**	**3 (< 0.1)**	**0.1**	**3**	**3 (< 0.1)**	**0.1**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Diplopia	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Iridocyclitis	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Uveitis	3	2 (< 0.1)	0.1	2	2 (< 0.1)	0.1	0	0	0.0	0	0	0.0
Musculoskeletal and connective tissue disorders	**6**	**6 (< 0.1)**	**0.1**	**3**	**3 (< 0.1)**	**0.1**	**5**	**3 (< 0.1)**	**0.2**	**5**	**5 (< 0.1)**	**0.1**
Ankylosing spondylitis	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	2	2 (< 0.1)	0.0
Arthralgia	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Arthritis	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Bursitis	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Myalgia	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Pain in extremity	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Polymyalgia rheumatica	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0	0	0	0.0	1	1 (< 0.1)	0.0
Rheumatoid arthritis	2	2 (< 0.1)	0.0	1	1 (< 0.1)	0.0	2	2 (< 0.1)	0.1	1	1 (< 0.1)	0.0
Sjogren's syndrome	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Systemic lupus erythematosus	0	0	0.0	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0
Nervous system disorders	**12**	**12 (< 0.1)**	**0.2**	**8**	**8 (< 0.1)**	**0.3**	**3**	**3 (< 0.1)**	**0.1**	**5**	**5 (< 0.1)**	**0.1**
Bell's palsy	3	3 (< 0.1)	0.1	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0	2	2 (< 0.1)	0.0
Hypoaesthesia	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Immune-mediated neuropathy	0	0	0.0	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0
Nervous system disorder	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Neuralgia	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0

Table 14: Potential Immune-Mediated Medical Conditions (PIMMCs) by Preferred Term for System Organ Classes with > 1 Participant Reporting an Event Based on Investigator Reporting and Protocol Defined Criteria in Study 301 (US/MX) (Safety Analysis Set)

	Pre-Crossover Period						Post-Crossover Period					
	NVX-CoV2373 N = 19735			Placebo N = 9847			NVX-CoV2373 N = 6416			Placebo N = 15298		
System Organ Class/ Preferred Term	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**	**E**	**N (%)**	**IR (e/100PY)**
Neuralgic amyotrophy	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Neuropathy peripheral	3	3 (< 0.1)	0.1	3	3 (< 0.1)	0.1	0	0	0.0	1	1 (< 0.1)	0.0
Paraesthesia	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Partial seizures	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Seizure	3	3 (< 0.1)	0.1	2	2 (< 0.1)	0.1	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0
Skin and subcutaneous tissue disorders	**4**	**4 (< 0.1)**	**0.1**	**3**	**2 (< 0.1)**	**0.1**	**4**	**3 (< 0.1)**	**0.2**	**2**	**2 (< 0.1)**	**0.0**
Alopecia	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Alopecia areata	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Dermatitis herpetiformis	0	0	0.0	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0
Erythema nodosum	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0	0	0	0.0
Lichen planus	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Lichenoid keratosis	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0	0	0	0.0
Pruritus	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Psoriasis	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Urticaria	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	0	0	0.0
Vitiligo	0	0	0.0	0	0	0.0	1	1 (< 0.1)	0.0	1	1 (<0.1)	0.0

e = Number of adverse events experienced, n = Unique number of participants experiencing the adverse event. e / 100 PY = Event Incidence rate per 100 person-years. The 95% CI = Exact Binomial Confidence Interval. N = Number of participants in the Safety Analysis Set within each treatment. Percentages or incidence proportion is based on n/N*100.
Adverse Events coded using MedDRA version 24.0.
Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date

7.4 Deaths, Other Serious Adverse Events, and Adverse Events Resulting in Discontinuation

7.4.1 Deaths

In Study 301 (US/MX), the overall frequency of deaths was low and balanced between study groups. A total of 11 (< 0.1%) participants in the NVX-CoV2373 group and 5 (< 0.1%) participants in the placebo group died during the pre-crossover period (Table 15). Rates were similarly low and balanced during the post-crossover period. None of the deaths were assessed by either the investigator or Sponsor as related to trial vaccine. Deaths within the SOC of Cardiac Disorders were the most frequent in both groups and occurred more frequently in the placebo group than the NVX-CoV2373 group both pre- and post-crossover. Cardiac arrest was the most frequent cause of death in both treatment groups.

Table 15: Summary of Unsolicited Adverse Events Leading to Death from Start of First Vaccination in All Participants in Study 301 (US/MX) (Safety Analysis Set)

System Organ Class Preferred Term (MedDRA, Version 24.0)	Pre-Crossover Period				Post-Crossover Period			
	NVX-CoV2373 N=19,735		Placebo N=9,847		NVX-CoV2373 N=6,416		Placebo N=15,298	
	e	n (%)	e	n (%)	e	n (%)	e	n (%)
Any System Organ Class	**11**	**11 (< 0.1)**	**5**	**5 (< 0.1)**	**6**	**6 (< 0.1)**	**11**	**10 (< 0.1)**
Cardiac disorders	**6**	**6 (< 0.1)**	**4**	**4 (< 0.1)**	**1**	**1 (< 0.1)**	**2**	**2 (< 0.1)**
Cardiac arrest	5	5 (< 0.1)	3	3 (< 0.1)	1	1 (< 0.1)	0	0
Cardiomyopathy alcoholic	0	0 (< 0.1)	0	0 (< 0.1)	0	0	1	1 (< 0.1)
Myocardial infarction	1	1 (< 0.1)	1	1 (< 0.1)	0	0	1	1 (< 0.1)
General disorders and administration site conditions	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**	**2**	**2 (< 0.1)**
Death	0	0	0	0	1	1 (< 0.1)	2	2 (< 0.1)
Hepatobiliary disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**
Hepatorenal syndrome	0	0	0	0	**0**	**0**	**1**	**1 (< 0.1)**
Infections and infestations	**1**	**1 (< 0.1)**	**1**	**1 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**
COVID-19 pneumonia	0	0	1	1 (< 0.1)	0	0	**0**	**0**
Septic shock	1	1 (< 0.1)	0	0	1	1 (< 0.1)	**0**	**0**
Injury, poisoning and procedural complications	**3**	**3 (< 0.1)**	**0**	**0**	**2**	**2 (< 0.1)**	**1**	**1 (< 0.1)**
Accidental overdose	1	1 (<0.1)	0	0	0	0	0	0
Gin shot wound	1	1 (<0.1)	0	0	0	0	0	0
Road traffic accident	0	0	0	0	1	1 (<0.1)	0	0
Toxicity to various agents	1	1 (<0.1)	0	0	1	1 (<0.1)	1	1 (<0.1)

Table 15: Summary of Unsolicited Adverse Events Leading to Death from Start of First Vaccination in All Participants in Study 301 (US/MX) (Safety Analysis Set)

System Organ Class Preferred Term (MedDRA, Version 24.0)	Pre-Crossover Period				Post-Crossover Period			
	NVX-CoV2373 N=19,735		Placebo N=9,847		NVX-CoV2373 N=6,416		Placebo N=15,298	
	e	n (%)	e	n (%)	e	n (%)	e	n (%)
Nervous system disorders	**1**	**1 (< 0.1)**	**0**	**0**	**0**	**0**	**1**	1 (<0.1)
Cerebrovascular accident	1	1 (<0.1)	0	0	0	0	0	0
Ischemic stroke	0	0	0	0	0	0	1	1 (< 0.1)
Psychiatric disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**
Completed suicide	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**2 (< 0.1)**
Chronic obstructive pulmonary disorder	0	0	0	0	0	0	2	2 (< 0.1)
Respiratory failure	0	0	0	0	0	0	1	1 (< 0.1)
Vascular disorders	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**	**0**	**0**
Aneurysm ruptured	0	0	0	0	1	1 (< 0.1)	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PP-EFF = Per-Protocol Efficacy; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein vaccine.

Note: Pre-crossover follow-up time is defined as the time from first dose to the earliest date of early termination, date of death and date of first crossover dose. For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and April 30, 2021. Post-crossover follow-up time is defined as the time from first crossover dose to the earliest date of early termination, date of booster dose, date of death, and date of the data cutoff date (September 27, 2021).

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

7.4.2 Other Serious Adverse Events

In Study 301 (US/MX), SAEs occurred infrequently in adults across both treatment groups and at generally similar frequencies (Table 16). SAEs of the SOCs Infections and Infestations, Cardiac Disorders, and Injury, Poisoning and Procedural Complications were the most frequent in both the NVX-CoV2373 and placebo groups. An imbalance was noted in the SOC Hepatobiliary Disorders driven by cholecystitis and acute cholecystitis; these events are discussed further in Section 7.5.1.

Table 16: Summary of SAEs by MedDRA Primary System Organ Class and Preferred Term for Events Reported for ≥ 3 Participants within a Treatment Group as of the Data Cutoff Date of September 27, 2021 in Study 301 (US/MX) (Safety Analysis Set)

Primary System Organ Class/ Preferred Term	Pre-Crossover Period				Post-Crossover Period			
	NVX-CoV2373 N = 19735		Placebo N = 9847		NVX-CoV2373 N = 6416		Placebo N = 15298	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Infections and infestations	**39 (0.2)**	**43**	**38 (0.4)**	**42**	**29 (0.5)**	**33**	**48 (0.3)**	**55**
Appendicitis	6 (< 0.1)	6	5 (< 0.1)	5	2 (< 0.1)	2	5 (< 0.1)	5
COVID-19	5 (< 0.1)	5	6 (< 0.1)	6	4 (< 0.1)	4	9 (< 0.1)	9
Pneumonia	4 (< 0.1)	4	4 (< 0.1)	4	4 (< 0.1)	4	3 (< 0.1)	3
Appendicitis perforated	3 (< 0.1)	3	1 (< 0.1)	1	0	0	1 (< 0.1)	1
Cellulitis	2 (< 0.1)	2	1 (< 0.1)	1	2 (< 0.1)	2	6 (< 0.1)	6
Sepsis	2 (< 0.1)	2	2 (< 0.1)	2	1 (< 0.1)	1	3 (< 0.1)	3
COVID-19 pneumonia	1 (< 0.1)	1	10 (0.1)	10	5 (< 0.1)	5	6 (< 0.1)	6
Osteomyelitis	1 (< 0.1)	1	0	0	0	0	3 (< 0.1)	3
Diverticulitis	0	0	2 (< 0.1)	2	0	0	3 (< 0.1)	3
Cardiac disorders	**33 (0.2)**	**38**	**17 (0.2)**	**17**	**13 (0.2)**	**14**	**21 (0.1)**	**25**
Atrial fibrillation	8 (< 0.1)	8	2 (< 0.1)	2	1 (< 0.1)	1	4 (< 0.1)	5
Cardiac arrest	5 (< 0.1)	5	3 (< 0.1)	3	1 (< 0.1)	1	0	0
Myocardial infarction	4 (< 0.1)	4	3 (< 0.1)	3	0	0	4 (< 0.1)	4
Cardiac failure congestive	3 (< 0.1)	3	1 (< 0.1)	1	0	0	3 (< 0.1)	3
Coronary artery disease	3 (< 0.1)	3	0	0	3 (< 0.1)	3	1 (< 0.1)	1
Acute myocardial infarction	2 (< 0.1)	2	3 (< 0.1)	3	5 (< 0.1)	5	2 (< 0.1)	2
Injury, poisoning and procedural complications	**24 (0.1)**	**27**	**15 (0.2)**	**16**	**5 (< 0.1)**	**5**	**16 (0.1)**	**20**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**21 (0.1)**	**21**	**6 (< 0.1)**	**6**	**10 (0.2)**	**10**	**21 (0.1)**	**21**
Prostate cancer	5 (< 0.1)	5	1 (< 0.1)	1	0	0	4 (< 0.1)	4
Breast cancer	3 (< 0.1)	3	0	0	1 (< 0.1)	1	2 (< 0.1)	2
Uterine leiomyoma	0	0	0	0	1 (< 0.1)	1	3 (< 0.1)	3
Intraductal proliferative breast lesion	0	0	0	0	0	0	3 (< 0.1)	3
Nervous system disorders	**20 (0.1)**	**21**	**7 (< 0.1)**	**7**	**4 (< 0.1)**	**4**	**11 (< 0.1)**	**12**
Cerebrovascular accident	6 (< 0.1)	6	0	0	0	0	1 (< 0.1)	1

Table 16: Summary of SAEs by MedDRA Primary System Organ Class and Preferred Term for Events Reported for ≥ 3 Participants within a Treatment Group as of the Data Cutoff Date of September 27, 2021 in Study 301 (US/MX) (Safety Analysis Set)

Primary System Organ Class/ Preferred Term	Pre-Crossover Period				Post-Crossover Period			
	NVX-CoV2373 N = 19735		Placebo N = 9847		NVX-CoV2373 N = 6416		Placebo N = 15298	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Respiratory, thoracic and mediastinal disorders	**17 (< 0.1)**	**20**	**7 (< 0.1)**	**7**	**10 (0.2)**	**10**	**17 (0.1)**	**22**
Pulmonary embolism	4 (< 0.1)	4	2 (< 0.1)	2	3 (< 0.1)	3	5 (< 0.1)	5
Pneumonia aspiration	4 (< 0.1)	4	0	0	0	0	0	0
Chronic obstructive pulmonary disease	3 (< 0.1)	3	1 (< 0.1)	1	2 (< 0.1)	2	3 (< 0.1)	6
Acute respiratory failure	3 (< 0.1)	3	0	0	0	0	2 (< 0.1)	2
Gastrointestinal disorders	**16 (< 0.1)**	**19**	**3 (< 0.1)**	**3**	**4 (< 0.1)**	**4**	**9 (< 0.1)**	**13**
Psychiatric disorders	**12 (< 0.1)**	**13**	**8 (< 0.1)**	**10**	**8 (0.1)**	**19**	**11 (< 0.1)**	**15**
Depression	4 (< 0.1)	4	0	0	0	0	3 (< 0.1)	3
Suicidal ideation	1 (< 0.1)	1	4 (< 0.1)	4	1 (< 0.1)	2	3 (< 0.1)	3
Hepatobiliary disorders	**11 (< 0.1)**	**14**	**1 (< 0.1)**	**2**	**12 (0.2)**	**13**	**5 (< 0.1)**	**5**
Cholecystitis acute	6 (< 0.1)	6	0	0	2 (< 0.1)	2	2 (< 0.1)	2
Cholecystitis	3 (< 0.1)	3	1 (< 0.1)	1	3 (< 0.1)	3	1 (< 0.1)	1
Cholecystitis chronic	0	0	0	0	3 (< 0.1)	3	0	0
Vascular disorders	**9 (< 0.1)**	**10**	**5 (< 0.1)**	**5**	**2 (< 0.1)**	**2**	**8 (< 0.1)**	**9**
Renal and urinary disorders	**9 (< 0.1)**	**9**	**4 (< 0.1)**	**4**	**3 (< 0.1)**	**4**	**7**	**0.2**
Acute kidney injury	7 (< 0.1)	7	2 (< 0.1)	2	1 (< 0.1)	2	4	0.1
Musculoskeletal and connective tissue disorders	**9 (< 0.1)**	**9**	**3 (< 0.1)**	**3**	**0**	**0**	**10 (< 0.1)**	**10**
Intervertebral disc protrusion	3 (< 0.1)	3	0	0	0	0	1 (< 0.1)	1
Osteoarthritis	1 (< 0.1)	1	2 (< 0.1)	2	0	0	3 (< 0.1)	3
General disorders and administration site conditions	**7 (< 0.1)**	**7**	**5 (< 0.1)**	**5**	**2 (< 0.1)**	**2**	**4 (< 0.1)**	**4**
Metabolism and nutrition disorders	**5 (< 0.1)**	**5**	**5 (< 0.1)**	**7**	**1 (< 0.1)**	**2**	**8 (< 0.1)**	**9**
Pregnancy, puerperium and perinatal conditions	**5 (< 0.1)**	**5**	**1 (< 0.1)**	**1**	**1 (< 0.1)**	**1**	**2 (< 0.1)**	**2**
Abortion spontaneous	4 (< 0.1)	4	0	0	1 (< 0.1)	1	2 (< 0.1)	2

Table 16: Summary of SAEs by MedDRA Primary System Organ Class and Preferred Term for Events Reported for ≥ 3 Participants within a Treatment Group as of the Data Cutoff Date of September 27, 2021 in Study 301 (US/MX) (Safety Analysis Set)

Primary System Organ Class/ Preferred Term	Pre-Crossover Period				Post-Crossover Period			
	NVX-CoV2373 N = 19735		Placebo N = 9847		NVX-CoV2373 N = 6416		Placebo N = 15298	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Blood and lymphatic system disorders	**4 (< 0.1)**	**4**	**0**	**0**	**0**	**0**	**2 (< 0.1)**	**3**
Reproductive system and breast disorders	**0**	**0**	**2 (< 0.1)**	**3**	**2 (< 0.1)**	**2**	**5 (< 0.1)**	**5**

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n/% = number/percentage of participants reporting the adverse event at least once [n] = number of events reported; N = number of participants included in the considered cohort in each group; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

1. Adverse Events coded using MedDRA version 24.0.

Note: AEs 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. Uncoded AEs are summarized as verbatim terms.

Note: Pre-crossover follow-up time is defined as the time from first dose to the earliest date of early termination, date of death and date of first crossover dose. For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and April 30, 2021. Post-crossover follow-up time is defined as the time from first crossover dose to the earliest date of early termination, date of booster dose, date of death, and date of the data cutoff date (September 27, 2021).

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

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7.4.3 Adverse Events Resulting in the Second Dose being Withheld

In Study 301 (US/MX), during the pre-crossover period, there was a slightly higher frequency of events of unsolicited AEs leading to the second dose being withheld in the NVX-CoV2373 group compared to placebo: 52 (0.3%) vs 23 (0.2%), respectively (Table 17). During the post-crossover period, such AEs were similarly low and balanced with both groups reporting < 0.1% of participants having their second dose withheld due to an AE.

Table 17: Summary of Unsolicited Adverse Events Resulting in the Second Dose being Withheld for At Least 2 Participants within a Treatment Group from Start of First Vaccination in All Participants in Study 301 (US/MX) (Safety Analysis Set)

System Organ Class Preferred Term (MedDRA, Version 23.1)	Pre-crossover Period				Post-crossover Period			
	NVX-CoV2373 N=19,735		Placebo N=9,847		NVX-CoV2373 N=6,416		Placebo N=15,298	
	e	n (%)	e	n (%)	e	n (%)	e	n (%)
Number of participants experiencing an event	**108**	**52 (0.3)**	**23**	**15 (0.2)**	**4**	**3 (< 0.1)**	**23**	**12 (< 0.1)**
Nervous system disorders	**15**	**11 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**	**7**	**5 (< 0.1)**
Headache	3	3 (0.1)	0	0	0	0	0	0
Dizziness	2	2 (< 0.1)	0	0	0	0	1	1 (< 0.1)
Lethargy	2	2 (< 0.1)	0	0	0	0	0	0
Paraesthesia	2	2 (< 0.1)	0	0	0	0	0	0
Infections and infestations	**14**	**11 (< 0.1)**	**6**	**5 (0.1)**	**1**	**1 (< 0.1)**	**2**	**2 (< 0.1)**
COVID-19	5	5 (< 0.1)	1	1 (< 0.1)	1	1 (< 0.1)	0	0
Pneumonia	2	2 (< 0.1)	1	1 (< 0.1)	0	0	0	0
General disorders and administration site conditions	**10**	**7 (< 0.1)**	**2**	**2 (< 0.1)**	0	0	0	1 (< 0.1)
Pyrexia	4	4 (< 0.1)	0	0	0	0	0	0
Fatigue	2	2 (< 0.1)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**12**	**9 (< 0.1)**	**3**	**3 (< 0.1)**	**0**	**0**	**2**	**2 (< 0.1)**
Cough	3	3 (< 0.1)	1	1 (< 0.1)	0	0	1	1 (< 0.1)
Dyspnoea	2	2 (< 0.1)	1	1 (< 0.1)	0	0	1	1 (< 0.1)
Nasal congestion	2	2 (< 0.1)	0	0	0	0	0	0
Gastrointestinal disorders	**11**	**10 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**	**2**	**1 (< 0.1)**
Diarrhoea	4	4 (< 0.1)	0	0	0	0	0	0
Nausea	3	3 (< 0.1)	0	0	0	0	0	0

Table 17: Summary of Unsolicited Adverse Events Resulting in the Second Dose being Withheld for At Least 2 Participants within a Treatment Group from Start of First Vaccination in All Participants in Study 301 (US/MX) (Safety Analysis Set)

System Organ Class Preferred Term (MedDRA, Version 23.1)	Pre-crossover Period				Post-crossover Period			
	NVX-CoV2373 N=19,735		Placebo N=9,847		NVX-CoV2373 N=6,416		Placebo N=15,298	
	e	n (%)	e	n (%)	e	n (%)	e	n (%)
Cardiac disorders	**6**	**5 (< 0.1)**	**3**	**3 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**
Cardiac arrest	2	2 (< 0.1)	2	2 (< 0.1)	0	0	0	0
Injury, poisoning and procedural complications	**6**	**4 (< 0.1)**	**1**	**1 (< 0.1)**	**1**	**1 (< 0.1)**	**3**	**2 (< 0.1)**
Investigations	**5**	**5 (< 0.1)**	**3**	**2 (< 0.1)**	**0**	**0**	**1**	**1 (< 0.1)**
Blood pressure increased	3	3 (< 0.1)	1	1 (< 0.1)	0	0	1	1 (< 0.1)
Musculoskeletal and connective tissue disorders	**5**	**5 (< 0.1)**	**0**	**0**	**1**	**1 (< 0.1)**	**4**	**2 (< 0.1)**
Renal and urinary disorders	**4**	**4 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**	**0**	**0**
Acute kidney injury	3	3 (< 0.1)	1	1 (< 0.1)	0	0	0	0
Skin and subcutaneous tissue disorders	**4**	**3 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**	**0**	**0**
Urticaria	2	2 (< 0.1)	0	0	0	0	0	0
Metabolism and nutrition disorders	**3**	**3 (< 0.1)**	**1**	**1 (< 0.1)**	**0**	**0**	**0**	**0**
Hypoglycaemia	2	2 (< 0.1)	0	0	0	0	0	0
Psychiatric disorders	**2**	**1 (< 0.1)**	**0**	**0**	**0**	**0**	**1**	**1 (< 0.1)**
Vascular disorders	**2**	**2 (< 0.1)**	**0**	**0**	**0**	**0**	**0**	**0**
Hypertension	2	2 (< 0.1)	0	0	0	0	0	0
Blood and lymphatic system disorders	**2**	**2 (< 0.1)**	**0**	**0**	**0**	**0**	**0**	**0**

Table 17: Summary of Unsolicited Adverse Events Resulting in the Second Dose being Withheld for At Least 2 Participants within a Treatment Group from Start of First Vaccination in All Participants in Study 301 (US/MX) (Safety Analysis Set)

System Organ Class Preferred Term (MedDRA, Version 23.1)	Pre-crossover Period				Post-crossover Period			
	NVX-CoV2373 N=19,735		Placebo N=9,847		NVX-CoV2373 N=6,416		Placebo N=15,298	
	e	n (%)	e	n (%)	e	n (%)	e	n (%)
Ear and labyrinth disorders	**2**	**2 (< 0.1)**	**0**	**0**	**0**	**0**	**0**	**0**
Vertigo	2	2 (< 0.1)	0	0	0	0	0	0
Eye disorders	2	2 (< 0.1)	0	0	0	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n/% = number/percentage of participants reporting the adverse event at least once [n] = number of events reported; N = number of participants included in the considered cohort in each group; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

Note: Adverse Events coded using MedDRA version 24.0.

Note: AEs 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. Uncoded AEs are summarized as verbatim terms.

Note: Pre-crossover follow-up time is defined as the time from first dose to the earliest date of early termination, date of death and date of first crossover dose. For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and April 30, 2021. Post-crossover follow-up time is defined as the time from first crossover dose to the earliest date of early termination, date of booster dose, date of death, and date of the data cutoff date (September 27, 2021).

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

7.5 Safety Events of Interest

Myocarditis/pericarditis, anaphylactic reaction, Guillain-Barré syndrome, and thrombosis with thrombocytopenia were investigated as possible safety events of interest because they were identified as potential risks of other SARS-CoV-2 vaccines. No cases of anaphylactic reaction, or thrombosis with thrombocytopenia have been reported in the NVX-CoV2373 development program. Recent follow-up on one case of neuropathy from Study 302 (UK) vaccine recipient provided details that met the Brighton Collaboration case definition for Guillain-Barré syndrome.

7.5.1 Cholecystitis Acute and Cholecystitis

Due to the imbalance noted in the primary safety analysis of the SOC Hepatobiliary Disorders driven primarily by cholecystitis, a thorough safety analysis was conducted. This analysis noted a higher incidence of SAEs of cholecystitis or acute cholecystitis in vaccine recipients compared to placebo. However, the overall frequency was low, and the RD was also low. Event rate per 100 PY in Study 301 (US/MX) was higher in vaccine recipients n = 9 (0.11 e/100 PY; 0.05%) than placebo recipients n = 1 (0.04; 0.01%) with a risk difference (RD) in rate per 100 PY of 0.07 (95% CI: 0.00, 0.14). The background rate is estimated to be 0.12 – 0.35 cases/100 PY, based on data from US administrative claims databases.

In the pooled safety data analysis of the SOC of Hepatobiliary Disorders from Day 0 to Day 49, sixteen events were reported in participants receiving active vaccine (N = 30,075) and 7 events in placebo-treated participants (N = 19,875). This represents 0.05% (95% CI: 0.03, 0.09) and 0.04% (95% CI: 0.01, 0.07) of participants in the active and placebo groups respectively, with a resulting RD of 0.02 (95% CI: -0.02, 0.06). The frequency of cholelithiasis is balanced between treatment groups, 8 (0.03%) participants in the NVX-CoV2373 group vs 3 (0.02%) participants in the placebo group. The proportions of other reported events within the SOC are generally balanced with small risk differences that lack consistent directionality (eg, active > placebo, or vice versa).

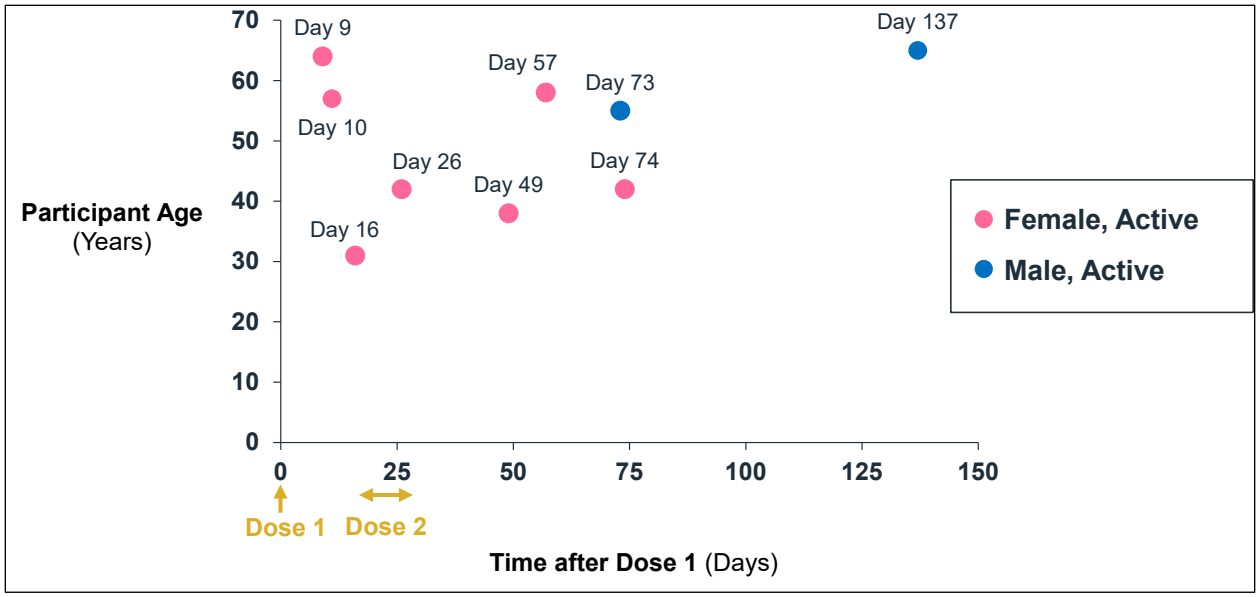
The incidence rates of SOC Hepatobiliary SAEs from Day 0 to End of Follow-up revealed 16 events (0.19 events/100 PY) in the NVX-CoV2373 group and 3 events (0.05 events/100 PY) in the placebo group with a RD of 0.11 (0.01, 0.22). Of these 16 SAEs, 12 were events of cholecystitis and 3 were events of cholelithiasis which occurred concurrently with cholecystitis. The remaining preferred terms were singular in nature or with an insignificant RD.

Although an inflammatory response may theoretically induce cholecystitis, there is no indication that NVX-CoV2373 would target end organs in the biliary tree and no indication there is a general inflammatory response that includes the biliary tree. The cases were primarily limited to the US population; if biliary inflammation were to be causally linked to vaccine administration, a more even distribution across the clinical program would be expected.

All cholecystitis events occurred in individuals with known risk factors for the condition. In particular, at the time of event onset, all participants had gallstones, which are unlikely to have

developed between vaccine administration and onset of cholecystitis. More than half (66%) of the individual events in Study 301 (US/MX) occurred more than 28 days following the last dose of vaccine administration. There was no obvious clustering or pattern of temporal relation observed. (Figure 14). The overall frequency of cholecystitis in the NVX-CoV2373 group is low (0.03%). Additionally, no imbalance is noted in the SOC of Hepatobiliary Disorders from Day 0 to 49.

Figure 14: Time to Onset of Cholecystitis SAE Following First Vaccination in Study 301 (US/MX) (Safety Analysis Set)



Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

A review of the clinical database for high level terms of Cholecystitis and Cholelithiasis did not reveal any imbalance in additional terms. A further analysis of the clinical database utilizing the Standardized MedDRA Query of Functional, Inflammatory, and Gallstone Related Biliary Disorders, both narrow and broad, revealed no clear evidence suggesting a treatment relationship between active vaccination and biliary disorders.

There have been no spontaneous reports of cholecystitis in the post-authorization setting in jurisdictions where NVX-CoV2373 is approved for use.

The totality of evidence does not support a causal link for the occurrence of cholecystitis and administration of NVX-CoV2373 vaccine.

7.5.2 Myocarditis/Pericarditis

In the placebo-controlled phases of the clinical program, myocarditis/pericarditis events were balanced in both the NVX-CoV2373 and placebo groups; 2 events (0.007%) in NVX-CoV2373 and 1 event (0.005%) in placebo. When evaluated with an exposure-adjusted IR per 100 PY (person-years); myocarditis/pericarditis cases in the NVX-CoV2373 group occurred at 0.03

events/100 PY compared with cases in placebo at 0.02 events/100 PY with a statistical risk difference of 0.00 (95% CI: -0.06, 0.07).

In the post-crossover phase of Study 301 (US/MX) and Study 302 (UK), three participants reported myocarditis/pericarditis. A background rate of myocarditis/pericarditis was determined utilizing data from ACCESS, a study funded by the EMA to determine background rates for COVID-19 vaccine AESIs. The total exposure to vaccine after the crossover, as of 31 October 2021 was 14,513 PY. The expected number of cases of myocarditis/pericarditis, as calculated based on ACCESS background rates ranged from 1.6 – 4.6 cases/14,513 PY. The observed rate of 3 cases/14,513 PY is within the range of expected background cases.

7.5.2.1 Spontaneous Reports of Myocarditis/Pericarditis

Spontaneous adverse event reports that are included in the Summary Safety Reports (SSRs) arise from the use of the vaccine in the real-world setting and are captured into surveillance systems similar to the FDA Vaccine Adverse Events Reporting System, from a variety of sources, including health care providers, vaccinees, the medical literature and social media posts. However, these passive reporting systems have many limitations, including underreporting, duplicate reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. These spontaneous reports may not be medically confirmed and are generally not verified.

The third monthly SSR submitted to global regulatory authorities on May 13, 2022 summarizes data received up to April 30, 2022. More than 740,000 doses of vaccine have been administered in Indonesia, Australia, EU, New Zealand and South Korea. The report included 35 spontaneous reports of suspected myocarditis or pericarditis, none of which met a definitive case definition. Ten reports met a probable case definition of pericarditis and 1 report met a probable case definition of myocarditis. All of the probable cases originated from Australia. Of the 10 probable pericarditis cases, 7 occurred in males, 3 in females and the age range was 25 to 58 years with a median of 41.5 years. Time to onset was unknown in 3 cases and ranged from 2 to 14 days following vaccination in the remaining 7 cases. The probable case of myocarditis occurred in a 47-year-old male with unknown time to onset. Many of these reports are missing important information including diagnostic workup. Two cases appear to be duplicates reports which, if confirmed, will reduce the total number of probable pericarditis cases to 8.

It is worth noting that there are currently a number of anomalies in the preliminary reporting of these cases. Most notably, all of the probable and possible cases that have been reported from Australia, a country that represents ~17% of the doses administered to date.

Novavax considers myocarditis/pericarditis to be an important potential risk and will continue to closely monitor and evaluate the data on this risk as they accrue.

7.6 Pregnancy

The use of NVX-CoV2373 vaccine in pregnancy and during breastfeeding has not been studied. Thus, there is limited experience with use of NVX-2373 in pregnant women. Available pregnancy data do not indicate a potential risk for the mother or fetus.

Pregnant or breastfeeding women were excluded from participation in all clinical studies with NVX- CoV2373. For women of childbearing potential, a urine pregnancy test was performed at Screening and prior to each study vaccination. A positive urine pregnancy test resulted in the participant not receiving study vaccination. 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. Pregnancy outcomes are summarized in Table 18.

Table 18: 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

	Total NVX-CoV2373 (N = 147)	**Time of Vaccination in Relation to Last Menstrual Period**			
		Before (N = 105)	**0-30 days after (N = 22)**	**> 30 days after (N = 9)**	**Unknown (N = 11)**
Pregnancy outcome	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	11	6	3	1	1

Note: Data current as of 15 March 2022.

8 PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY PLAN

The pharmacovigilance strategies outlined in the Pharmacovigilance Plan are designed to address potential safety concerns in the post registration setting.

Routine and enhanced pharmacovigilance include Monthly Summary Safety Reports, targeted follow-up questionnaires, and daily/weekly/monthly qualitative and quantitative reviews using multiple data sources for signal detection. In addition, five post-authorization real-world studies will be conducted:

- 2019nCoV-401 = Novavax COVID-19 Vaccine Effectiveness Against Severe COVID-19 in Europe using COVIDRIVE platform
- 2019nCoV-402 = Post-Authorization Safety Study using the Clinical Practice Research Database (CPRD) in the UK
- 2019nCoV-403 = Post-Authorization Effectiveness Study Using a Claims and/or Electronic Health Database in the US
- 2019nCoV-404 = Post-Authorization Safety Study Using a Claims and/or Electronic Health Database in the US
- 2019nCoV-405 = COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

These real-world studies conducted in the US and internationally will collect additional data that will inform the safety and effectiveness of NVX-CoV2373.In the post-authorization setting, greater than 700,000 doses of vaccine have been administered in Indonesia, Australia, European Union, New Zealand, and South Korea.

9 BENEFIT-RISK CONCLUSIONS

The primary efficacy objective of the Phase 3 Clinical Study 301 (US) was achieved, with the VE of NVX-CoV2373 to prevent PCR-confirmed symptomatic mild, moderate, or severe COVID-19 shown to be 90.4%.

The vaccine showed high levels of efficacy in subgroup analyses performed by race and sex and in individuals at high risk of COVID-19, either due to underlying comorbidities or due to increased exposure to SARS-CoV-2. The vaccine was also observed to be efficacious in preventing moderate or severe COVID-19, with no NVX-CoV2373 recipient experiencing moderate or severe COVID-19 with an onset from at least 7 days after second vaccination.

The vaccine demonstrated efficacy against SARS-CoV-2 strains more closely matched to the vaccine strain as well as against variants that circulated during the studies. For the more closely matched strains, efficacy of the vaccine was 100% for strains not considered a variant of concern or interest in Study 301 (US/MX). Vaccine efficacy for strains that were considered either a variant of concern or interest was 93.2% in Study 301 (US/MX) and efficacy for the B.1.1.7 (Alpha) variant was 93.6%, in that study.

Based on the administration of NVX-CoV2373 to 30,058 adults across the SARS-CoV-2 rS clinical development program, there is a reassuring safety profile and favorable reactogenicity profile. Most common among these reactions was pain/tenderness at the injection site and systemic events of fatigue, muscle pain, and headache. Although the incidence of unsolicited AEs was slightly higher in the NVX-CoV2373 group than in the placebo group, the difference was largely due to reactogenicity-like events. SAEs and deaths occurred in few participants, with similar events for placebo and vaccine recipients that were generally balanced across treatment groups.

Based on the totality of the data across the SARS-CoV-2 rS clinical development program, NVX-CoV2373 administered as two IM injections at 3 weeks apart is an effective vaccine with an acceptable safety profile for active immunization for the prevention of COVID-19 caused by SARS-CoV-2. Considering the ongoing public health emergency due to SARS-CoV-2 and its emerging variants, the need for additional effective vaccines, and the available efficacy, immunogenicity, and safety data across the NVX-CoV2373 clinical development program, the Sponsor considers that the known and potential benefits of the product outweigh the known and potential risks of the proposed vaccine and warrant consideration for authorization.

10 REFERENCES

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11 APPENDICES

11.1 Appendix: Phase 3 Study 301 (US/MX) – Enrollment Criteria (Protocol Version 10.0 – 11 October 2021)

Included in this section are the enrollment criteria applicable to adult participants in Phase 3 Study 301 (US/MX).

Inclusion Criteria

Each participant in the Adult Main Study must have meet all of the following criteria to be enrolled in this study:

1. Adults ≥ 18 years of age at screening who, by virtue of age, race, ethnicity or life circumstances, are considered at substantial risk of exposure to and infection with SARSCoV-2.
2. Willing and able to give informed consent prior to study enrollment and to comply with study procedures.
3. Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile [i.e., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months]) must agree to be heterosexually inactive from at least 28 days prior to enrollment and through 3 months after the last vaccination OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through 3 months after the last vaccination.
4. Is medically stable, as determined by the investigator (based on review of health status, vital signs [to include body temperature], medical history, and targeted physical examination [to include body weight]). Vital signs must be within medically acceptable ranges prior to the first vaccination.
5. Agree to not participate in any other SARS-CoV-2 prevention trial during the study follow-up.
6. Active participants who received a full dose regimen of commercial COVID-19 vaccine during the course of study participation are eligible for participation in the Adult Main Study with Booster Amendment. Such participants must demonstrate receipt by producing a CDC-supplied vaccination card ahead of the booster visit.

Exclusion Criteria

Adult participants meeting any of the following criteria were to be excluded from the study:

1. Unstable acute or chronic illness. Criteria for unstable medical conditions include:
   a. Substantive changes in chronic prescribed medication (change in class or significant change in dose) in the past 2 months.
   b. Currently undergoing workup of undiagnosed illness that could lead to diagnosis of a new condition.

   Note: Well-controlled human immunodeficiency virus [HIV] with undetectable HIV RNA [< 50 copies/mL] and CD4 count > 200 cells/μL for at least 1 year, documented within the last 6 months, is NOT considered an unstable chronic illness. Participant's or parent's/caregiver's verbal report will suffice as documentation.
2. Participation in research involving an investigational product (drug/biologic/device) administered within 45 days prior to first study vaccination.
3. History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19. A previous diagnosis of COVID-19 during participation in this trial is not exclusionary for the Adult Main Study with Booster Amendment.
4. Received any vaccine within 4 days prior to first study vaccination or planned receipt of any vaccine before Day 49 (i.e., 28 days after second vaccination), except for influenza vaccination, which may be received ≥ 4 days prior to or ≥ 7 days after either study vaccination. Rabies vaccine, at any time it is medically indicated, is not exclusionary. Prior receipt of another approved or authorized COVID-19 vaccine prior to booster injection is not exclusionary in the Adult Main Study with Booster Amendment. Such participants must provide documentation of vaccine and date(s) of administration.
5. Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression.

   NOTE: Stable endocrine disorders (eg, thyroiditis, pancreatitis, including stable diabetes mellitus) are NOT excluded.
6. Chronic administration (defined as > 14 continuous days) of immunosuppressant or systemic glucocorticoids causing clinically significant immunocompromise, within 90 days prior to first study vaccination.

   NOTE: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 20 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids is permitted. Topical tacrolimus and ocular cyclosporin are permitted.

7. Received immunoglobulin or blood-derived products, within 90 days prior to first study vaccination.
8. Active cancer (malignancy) on chemotherapy that is judged to cause clinically significant immunocompromise within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator). This criterion is not applicable to participants diagnosed during participation in this trial who accept participation in the Adult Main Study with Booster Amendment.
9. Any known allergies to products contained in the investigational product.
10. Participants who are breastfeeding, pregnant or who plan to become pregnant within 3 months following last study vaccination.
11. Any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled or could interfere with evaluation of the trial vaccine or interpretation of study results.
12. Study team member or first-degree relative of any study team member (inclusive of Sponsor, and study site personnel involved in the study).
13. Current participation in any other COVID-19 prevention clinical trial.
14. Adult participants who have not received a full dose of any commercial COVID-19 vaccine and are unable to provide a CDC Vaccination Card will be excluded from the Adult Main Study with Booster Amendment.

11.2 Appendix: Additional Safety Tables

Demographics and baseline characteristics for participants included in the Safety Analysis Set for Study 301 (US/MX) are summarized in Table 19.

Table 19: Study 301 (US/MX) - Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristic	Pre-Crossover Period			Post-Crossover Period		
	NVX-CoV2373 N = 19735	**Placebo N = 9847**	**Total N = 29945**	**NVX-CoV2373 N = 6416**	**Placebo N = 15298**	**Total N = 21714**
Sex, n (%)						
Male	10367 (52.5)	5019 (51.0)	15386 (52.0)	3191 (49.7)	7913 (51.7)	11104 (51.1)
Female	9368 (47.5)	4828 (49.0)	14196 (48.0)	3225 (50.3)	7385 (48.3)	10610 (48.9)
Age (years)						
Mean (SD)	46.5 (15.05)	46.8 (14.95)	46.6 (15.02)	46.3 (14.86)	46.1 (14.82)	46.1 (14.83)
Median	47.0	47.0	47.0	47.0	46.0	46.0
Min, max	18, 95	18, 90	18, 95	18, 90	18, 95	18, 95
Age subgroups, n (%)						
18 to < 65 years	17255 (87.4)	8612 (87.5)	25867 (87.4)	5686 (88.6)	13576 (88.7)	19262 (88.7)
≥ 65 years	2480 (12.6)	1235 (12.5)	3715 (12.6)	730 (11.4)	1722 (11.3)	2452 (11.3)
Race, n (%)						
White	14794 (75.0)	7381 (75.0)	22175 (75.0)	4651 (72.5)	11393 (74.5)	16044 (73.9)
Black or African American	2323 (11.8)	1164 (11.8)	3487 (11.8)	880 (13.7)	1811 (11.8)	2691 (12.4)
American Indian or Alaska Native[1]	1309 (6.6)	661 (6.7)	1970 (6.7)	468 (7.3)	1049 (6.9)	1517 (7.0)
Asian	810 (4.1)	416 (4.2)	1226 (4.1)	254 (4.0)	637 (4.2)	891 (4.1)
Multiple	325 (1.6)	159 (1.6)	484 (1.6)	116 (1.8)	272 (1.8)	388 (1.8)
Native Hawaiian or Other Pacific Islander	56 (0.3)	12 (0.1)	68 (0.2)	8 (0.1)	40 (0.3)	48 (0.2)
Not reported	110 (0.6)	47 (0.5)	157 (0.5)	34 (0.5)	89 (0.6)	123 (0.6)
Missing	8 (< 0.1)	7 (< 0.1)	15 (< 0.1)	5 (< 0.1)	7 (< 0.1)	12 (< 0.1)
Ethnicity, n (%)						
Not Hispanic or Latino	15345 (77.8)	7669 (77.9)	23014 (77.8)	4898 (76.3)	11800 (77.1)	16698 (76.9)
Hispanic or Latino	4334 (22.0)	2155 (21.9)	6489 (21.9)	1501 (23.4)	3453 (22.6)	4954 (22.8)
Not reported	32 (0.2)	19 (0.2)	51 (0.2)	14 (0.2)	24 (0.2)	38 (0.2)
Missing or unknown	24 (0.1)	4 (< 0.1)	28 (< 0.1)	3 (< 0.1)	21 (0.1)	24 (0.1)
Country, n (%)						
Mexico	1176 (6.0)	588 (6.0)	1764 (6.0)	427 (6.7)	990 (6.5)	1417 (6.5)
United States	18559 (94.0)	9259 (94.0)	27818 (94.0)	5989 (93.3)	14308 (93.5)	20297 (93.5)
Occupational risk, n (%)						
Work requires close proximity to others	7796 (39.5)	3798 (38.6)	11594 (39.2)	2520 (39.3)	6146 (40.2)	8666 (39.9)
Comorbidities, n (%)						
Obesity (BMI: > 30 kg/m^2)	7289 (36.9)	3668 (37.2)	10957 (37.0)	2603 (40.6)	5765 (37.7)	8368 (38.5)
Chronic kidney disease	149 (0.8)	64 (0.6)	213 (0.7)	49 (0.8)	111 (0.7)	160 (0.7)

Table 19: Study 301 (US/MX) - Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristic	Pre-Crossover Period			Post-Crossover Period		
	NVX-CoV2373 N = 19735	Placebo N = 9847	Total N = 29945	NVX-CoV2373 N = 6416	Placebo N = 15298	Total N = 21714
Chronic lung disease	2776 (14.1)	1446 (14.7)	4222 (14.3)	950 (14.8)	2170 (14.2)	3120 (14.4)
Cardiovascular disease	226 (1.1)	126 (1.3)	352 (1.2)	77 (1.2)	168 (1.1)	245 (1.1)
Diabetes mellitus type 2	1525 (7.7)	814 (8.3)	2339 (7.9)	587 (9.1)	1197 (7.8)	1784 (8.2)
High risk Adults[2], n (%)						
Yes	18811 (95.3)	9378 (95.2)	28189 (95.3)	6126 (95.5)	14586 (95.3)	20712 (95.4)
No	924 (4.7)	469 (4.8)	1393 (4.7)	290 (4.5)	712 (4.7)	1002 (4.6)
Baseline SARS-CoV-2 status (Anti-NP or PCR)						
Negative	18462 (93.5)	9156 (93.0)	27618 (93.4)	5886 (91.7)	14306 (93.5)	20192 (93.0)
Positive	1273 (6.5)	691 (7.0)	1964 (6.6)	530 (8.3)	992 (6.5)	1522 (7.0)

Abbreviations: BMI = body mass index; eCRF = electronic case report form; max = maximum; min = minimum; NP = nucleocapsid protein; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation; US = United States.

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 American Indians enrolled at sites in the US.
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.

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 20: Solicited Local Adverse Events Reported Within 7 Days of Each Vaccination in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 18135 n (%)	Placebo Dose 1 N = 8982 n (%)	NVX-CoV2373 Dose 2 N = 17196 n (%)	Placebo Dose 2 N = 8339 n (%)
Pain/tenderness				
Any (Grade ≥ 1)	10458 (57.67)	1881 (20.94)	13492 (78.46)	1784 (21.39)
Grade 3	187 (1.03)	20 (0.22)	994 (5.78)	21 (0.25)
Grade 4	0	0	5 (0.03)	1 (0.1)
Erythema				
Any (Grade ≥ 1)	167 (0.92)	26 (0.29)	1139 (6.62)	30 (0.36)
Grade 3	3 (0.02)	0	141 (0.82)	2 (0.02)
Grade 4	0	0	0	0
Swelling				
Any (Grade ≥ 1)	155 (0.85)	25 (0.28)	1054 (6.13)	26 (0.31)
Grade 3	8 (0.04)	3 (0.03)	90 (0.52)	2 (0.02)
Grade 4	0	0	0	0

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 21: Solicited Local Adverse Events Reported Within 7 Days of Each Vaccination in Participants 18 to 64 Years of Age in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 15884 n (%)	Placebo Dose 1 N = 7868 n (%)	NVX-CoV2373 Dose 2 N = 15148 n (%)	Placebo Dose 2 N = 7361 n (%)
Pain/tenderness				
Any (Grade ≥ 1)	9604 (60.46)	1706 (21.68)	12234 (80.76)	1623 (22.05)
Grade 3	174 (1.10)	17 (0.22)	951 (6.28)	20 (0.27)
Grade 4	0	0	5 (0.03)	1 (0.01)
Erythema				
Any (Grade ≥ 1)	151 (0.95)	21 (0.27)	1040 (6.87)	26 (0.35)
Grade 3	3 (0.02)	0	134 (0.88)	2 (0.03)
Grade 4	0	0	0	0
Swelling				
Any (Grade ≥ 1)	137 (0.86)	24 (0.31)	943 (6.23)	22 (0.30)
Grade 3	6 (0.04)	3 (0.04)	82 (0.54)	1 (0.01)
Grade 4	0	0	0	0

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 22: Solicited Local Adverse Events Reported Within 7 Days of Each Vaccination in Participants ≥ 65 Years of Age in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 2251 n (%)	Placebo Dose 1 N = 1114 n (%)	NVX-CoV2373 Dose 2 N = 2048 n (%)	Placebo Dose 2 N = 978 n (%)
Pain/tenderness				
Any (Grade ≥ 1)	854 (37.94)	175 (15.71)	1258 (61.43)	161 (16.46)
Grade 3	13 (0.58)	3 (0.27)	43 (2.10)	1 (0.10)
Grade 4	0	0	0	0
Erythema				
Any (Grade ≥ 1)	16 (0.71)	5 (0.45)	99 (4.83)	4 (0.41)
Grade 3	0	0	7 (0.34)	0
Grade 4	0	0	0	0
Swelling				
Any (Grade ≥ 1)	18 (0.80)	1 (0.09)	111 (5.42)	4 (0.41)
Grade 3	1 (0.04)	0	8 (0.39)	1 (0.10)
Grade 4	0	0	0	0

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 23: Solicited Systemic Adverse Events Reported Within 7 Days of Each Vaccination in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 18131 n (%)	Placebo Dose 1 N = 8981 n (%)	NVX-CoV2373 Dose 2 N = 17180 n (%)	Placebo Dose 2 N = 8338 n (%)
Any solicited systemic reaction				
Any (Grade ≥ 1)	8607 (47.47)	3589 (39.96)	11908 (69.31)	2988 (35.84)
Grade 3	417 (2.30)	187 (2.08)	2054 (11.96)	170 (2.04)
Grade 4	15 (0.08)	4 (0.04)	18 (0.10)	5 (0.06)
Fever				
Any (Grade ≥ 1)	62 (0.34)	34 (0.38)	968 (5.63)	23 (0.28)
Grade 1	35 (0.19)	18 (0.20)	641 (3.73)	16 (0.19)
Grade 2	15 (0.08)	8 (0.09)	264 (1.54)	4 (0.05)
Grade 3	8 (0.04)	7 (0.08)	61 (0.36)	3 (0.04)
Grade 4	4 (0.02)	1 (0.01)	2 (0.01)	0
Headache				
Any (Grade ≥ 1)	4499 (24.81)	2047 (22.79)	7623 (44.37)	1636 (19.62)
Grade 1	3446 (19.01)	1590 (17.70)	4151 (24.16)	1220 (14.63)
Grade 2	905 (4.99)	394 (4.39)	2957 (17.21)	376 (4.51)
Grade 3	143 (0.79)	62 (0.69)	509 (2.96)	38 (0.46)
Grade 4	5 (0.03)	1 (0.01)	6 (0.03)	2 (0.02)
Fatigue/malaise				
Any (Grade ≥ 1)	5335 (29.42)	2296 (25.57)	9537 (55.51)	2071 (24.84)
Grade 1	2642 (14.57)	1135 (12.64)	2858 (16.64)	986 (11.83)
Grade 2	2414 (13.31)	1042 (11.60)	5014 (29.19)	955 (11.45)
Grade 3	271 (1.49)	118 (1.31)	1658 (9.65)	127 (1.52)
Grade 4	8 (0.04)	1 (0.01)	7 (0.04)	3 (0.04)
Muscle pain (myalgia)				
Any (Grade ≥ 1)	4107 (22.65)	1196 (13.32)	8238 (47.95)	1002 (12.02)
Grade 1	3050 (16.82)	842 (9.38)	3812 (22.19)	681 (8.17)
Grade 2	973 (5.37)	318 (3.54)	3584 (20.86)	287 (3.44)
Grade 3	82 (0.45)	35 (0.39)	837 (4.87)	30 (0.36)
Grade 4	2 (0.01)	1 (0.01)	5 (0.03)	4 (0.05)
Joint pain (arthralgia)				
Any (Grade ≥ 1)	1395 (7.69)	591 (6.58)	3811 (22.18)	565 (6.78)
Grade 1	860 (4.74)	360 (4.01)	1627 (9.47)	349 (4.19)
Grade 2	482 (2.66)	202 (2.25)	1769 (10.30)	190 (2.28)
Grade 3	52 (0.29)	29 (0.32)	409 (2.38)	24 (0.29)
Grade 4	1 (< 0.01)	0	6 (0.03)	2 (0.02)
Nausea/vomiting				
Any (Grade ≥ 1)	1149 (6.34)	497 (5.53)	1926 (11.21)	451 (5.41)
Grade 1	918 (5.06)	389 (4.33)	1386 (8.07)	344 (4.13)
Grade 2	210 (1.16)	99 (1.10)	505 (2.94)	98 (1.18)
Grade 3	17 (0.09)	7 (0.08)	28 (0.16)	7 (0.08)
Grade 4	4 (0.02)	2 (0.02)	7 (0.04)	2 (0.02)

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 24: Solicited Systemic Adverse Events Reported Within 7 Days of Each Vaccination in Participants 18 to 64 Years of Age in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 15884 n (%)	Placebo Dose 1 N = 7868 n (%)	NVX-CoV2373 Dose 2 N = 15148 n (%)	Placebo Dose 2 N = 7361 n (%)
Fever				
Any (Grade ≥ 1)	56 (0.35)	31 (0.39)	941 (6.21)	16 (0.22)
Grade 1	32 (0.20)	16 (0.20)	621 (4.10)	11 (0.15)
Grade 2	13 (0.08)	7 (0.09)	258 (1.70)	3 (0.04)
Grade 3	7 (0.04)	7 (0.09)	60 (0.40)	2 (0.03)
Grade 4	4 (0.03)	1 (0.01)	2 (0.01)	0
Headache				
Any (Grade ≥ 1)	4158 (26.18)	1866 (23.72)	7128 (47.06)	1492 (20.27)
Grade 1	3155 (19.86)	1438 (18.28)	3777 (24.93)	1102 (14.97)
Grade 2	867 (5.46)	369 (4.69)	2855 (18.85)	352 (4.78)
Grade 3	132 (0.83)	58 (0.74)	491 (3.24)	36 (0.49)
Grade 4	4 (0.03)	1 (0.01)	5 (0.03)	2 (0.03)
Fatigue/malaise				
Any (Grade ≥ 1)	4892 (30.80)	2095 (26.63)	8825 (58.26)	1889 (25.66)
Grade 1	2396 (15.08)	1031 (13.10)	2565 (16.93)	890 (12.09)
Grade 2	2239 (14.10)	950 (12.07)	4662 (30.78)	882 (11.98)
Grade 3	249 (1.57)	113 (1.44)	1591 (10.50)	114 (1.55)
Grade 4	8 (0.05)	1 (0.01)	7 (0.05)	3 (0.04)
Muscle pain (myalgia)				
Any (Grade ≥ 1)	3827 (24.09)	1073 (13.64)	7682 (50.71)	900 (12.23)
Grade 1	2831 (17.82)	756 (9.61)	3471 (22.91)	613 (8.33)
Grade 2	915 (5.76)	285 (3.62)	3401 (22.45)	255 (3.46)
Grade 3	79 (0.50)	31 (0.39)	805 (5.31)	28 (0.38)
Grade 4	2 (0.01)	1 (0.01)	5 (0.03)	4 (0.05)
Joint pain (arthralgia)				
Any (Grade ≥ 1)	1260 (7.93)	522 (6.63)	3542 (23.38)	504 (6.85)
Grade 1	776 (4.89)	323 (4.11)	1488 (9.82)	317 (4.31)
Grade 2	434 (2.73)	174 (2.21)	1656 (10.93)	163 (2.21)
Grade 3	49 (0.31)	25 (0.32)	393 (2.59)	22 (0.30)
Grade 4	1 (< 0.01)	0	5 (0.03)	2 (0.03)
Nausea/vomiting				
Any (Grade ≥ 1)	1069 (6.73)	466 (5.92)	1822 (12.03)	417 (5.66)
Grade 1	850 (5.35)	364 (4.63)	1305 (8.61)	317 (4.31)
Grade 2	198 (1.25)	93 (1.18)	484 (3.20)	91 (1.24)
Grade 3	17 (0.11)	7 (0.09)	26 (0.17)	7 (0.10)
Grade 4	4 (0.03)	2 (0.03)	7 (0.05)	2 (0.03)

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 25: Solicited Systemic Adverse Events Reported Within 7 Days of Each Vaccination in Participants ≥ 65 Years of Age in Study 301 (US/MX) (Ad Hoc Dataset)

Event	NVX-CoV2373 Dose 1 N = 2251 n (%)	Placebo Dose 1 N = 1114 n (%)	NVX-CoV2373 Dose 2 N = 2048 n (%)	Placebo Dose 2 N = 978 n (%)
Fever				
Any (Grade ≥ 1)	8 (0.36)	3 (0.27)	40 (1.95)	7 (0.72)
Grade 1	4 (0.18)	2 (0.18)	30 (1.46)	5 (0.51)
Grade 2	3 (0.13)	1 (0.09)	8 (0.39)	1 (0.10)
Grade 3	1 (0.04)	0	2 (0.10)	1 (0.10)
Grade 4	0	0	0	0
Headache				
Any (Grade ≥ 1)	344 (15.28)	184 (16.52)	502 (24.51)	144 (14.72)
Grade 1	292 (12.97)	153 (13.73)	378 (18.46)	118 (12.07)
Grade 2	39 (1.73)	27 (2.42)	105 (5.13)	24 (2.45)
Grade 3	12 (0.53)	4 (0.36)	18 (0.88)	2 (0.20)
Grade 4	1 (0.04)	0	1 (0.05)	0
Fatigue/malaise				
Any (Grade ≥ 1)	444 (19.72)	202 (18.13)	714 (34.86)	182 (18.61)
Grade 1	246 (10.93)	105 (9.43)	295 (14.40)	96 (9.82)
Grade 2	175 (7.77)	92 (8.26)	351 (17.14)	73 (7.46)
Grade 3	23 (1.02)	5 (0.45)	68 (3.32)	13 (1.33)
Grade 4	0	0	0	0
Muscle pain (myalgia)				
Any (Grade ≥ 1)	284 (12.62)	125 (11.22)	561 (27.39)	102 (10.43)
Grade 1	222 (9.86)	88 (7.90)	344 (16.80)	68 (6.95)
Grade 2	59 (2.62)	33 (2.96)	185 (9.03)	32 (3.27)
Grade 3	3 (0.13)	4 (0.36)	32 (1.56)	2 (0.20)
Grade 4	0	0	0	0
Joint pain (arthralgia)				
Any (Grade ≥ 1)	139 (6.18)	71 (6.37)	271 (13.23)	63 (6.44)
Grade 1	86 (3.82)	39 (3.50)	141 (6.88)	34 (3.48)
Grade 2	49 (2.18)	28 (2.51)	113 (5.52)	27 (2.76)
Grade 3	4 (0.18)	4 (0.36)	16 (0.78)	2 (0.20)
Grade 4	0	0	1 (0.05)	0
Nausea/vomiting				
Any (Grade ≥ 1)	81 (3.60)	32 (2.87)	108 (5.27)	35 (3.58)
Grade 1	69 (3.07)	26 (2.33)	84 (4.10)	28 (2.86)
Grade 2	12 (0.53)	6 (0.54)	21 (1.03)	7 (0.72)
Grade 3	0	0	3 (0.15)	0
Grade 4	0	0	0	0

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.

Table 26: Frequency of Unsolicited AEs Reported Within 49 Days with Occurrence in ≥ 1% of Participants in Any Treatment Group in Clinical Study 2019nCoV-301 as of the Data Cutoff Date of September 27, 2021 (Ad Hoc Dataset)

Primary System Organ Class/ Preferred Term[1]	NVX-CoV2373		Placebo	
	Any n/N (%)	Severe n/N (%)	Any n/N (%)	Severe n/N (%)
Pre-crossover period				
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)
Post-crossover period				
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)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n/% = number/percentage of participants reporting the adverse event at least once [n] = number of events reported; N = number of participants included in the considered cohort in each group; NVX-CoV2373 = 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

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).

Note: 27 September 2021 data cutoff date; 17 February 2022 data extraction date.