Application Type	Original BLA
STN	125817/0
CBER Received Date	April 1, 2024
PDUFA Goal Date	April 1, 2025
Clinical Reviewers	Charles Line, MD Amina White, MD
Project Manager	CAPT Edward Wolfgang, PhD Paul Keller, PhD Donna Elhindi, PharmD
Priority Review	No
Reviewer Name	Rositsa Dimova, PhD
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, PhD Concurring Reviewer, VEB, DB, OBPV
	Tsai-Lien Lin, PhD Chief, VEB, DB, OBPV
	John Scott, PhD Director, DB, OBPV
Applicant	Novavax, Inc.
Established Name	Novavax COVID-19 Vaccine, Adjuvanted
(Proposed) Trade Name	Nuvaxovid
Pharmacologic Class	COVID-19 Vaccine
Formulation(s), including Adjuvants, etc	5 µg recombinant spike protein and 50 µg Matrix-M adjuvant
Dosage Form(s) and Route(s) of Administration	0.5 mL dose administered intramuscularly
Dosing Regimen	A single 0.5 mL dose
Indication(s) and Intended Population(s)	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

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GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
BLA	Biologics License Application
CBER	Center for Biologics Evaluation, Research and Review
CDER	Center for Drugs Evaluation, Research and Review
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
IR	Information Request
IR	Incidence Rate
LB	Lower Bound
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
mRNA	Messenger Ribonucleic Acid
PCR	Polymerase Chain Reaction
PP-EFF	Per-protocol Efficacy
PP-IMM	Per-protocol Immunogenicity
PT	Preferred Term
RCT	Randomized Controlled Trial
RD	Risk Difference
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	Sero-conversion Rate
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UK	United Kingdom
US	United States
VE	Vaccine Efficacy

1. Executive Summary

Novavax, Inc. submitted an original Biologics License Application (BLA) on April 1, 2024 (STN 125817/0) for their Novavax COVID-19 Vaccine, Adjuvanted (also referred to as SARS-CoV-2 rS and NVX-CoV-2373 in this review memo) for the indication of prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

The ongoing pivotal phase 3 study 2019nCoV-301, entitled "A Phase 3, Randomized, Observer-Blinded, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-COV-2 Recombinant Spike Protein Nanoparticle Vaccine (Sars-CoV-2 rS) with Matrix-M1 Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years)" serves as the primary evidence of effectiveness and safety for the sought indication. The Adults Main study and Pediatric Expansion in adolescents are reviewed separately in this memo.

The Adult Main Study was a randomized, observer-blinded, placebo-controlled, crossover study in adults 18 years of age or older. The study included 3 vaccination periods - an Initial Vaccination Period, Crossover Period and a Booster Period. In the Initial Vaccination Period (also referred to as Pre-crossover Period), subjects were randomized in a 2:1 ratio to receive a primary series of 2 doses (21 days apart) of NVX-CoV2373 or placebo. In the blinded Crossover Period (approximately 2 months after completion of the primary series), participants were offered to receive 2 injections of the alternate product (21 days apart) in a blinded manner. Additionally, participants were to be offered to receive a single dose of NVX-CoV2373 at least 6 months after completion of active vaccination in the Booster Vaccination Period. The primary efficacy objective was to evaluate the efficacy of NVX-CoV-2373 (Original Wuhan strain formulation) against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 (with onset from at least 7 days after second vaccination). The data and analyses submitted in this application were based on a data cutoff date of August 18, 2022 for the Adults portion, and a data cutoff date of August 6, 2022 for the Adolescents portion.

In the Adults portion of this study, a total of 29943 subjects were randomized (2:1 ratio) to receive 2 doses (21 days apart) of NVXCoV2373 (N=19961) or placebo (N=9982) in the Initial Vaccination Period. Of the randomized subjects, respectively, 19735 received at least 1 dose of NVXCoV2373 and 9847 received placebo. During the blinded Crossover Period, a total of 6416 subjects received at least 1 dose of NVX-CoV2373, and a total of 15298 subjects received only placebo. A total of 13,353 participants received a booster dose of NVX-CoV2373 at least 6 months after completion of their active primary series vaccination. The primary efficacy endpoint was derived based on the investigator assessments (including severity and start date) and a PCR test results from a central laboratory during the Initial Vaccination Period. It was defined as the first occurrence of mild, moderate or severe PCR-positive COVID-19 starting during the period from 7 days after the second vaccine dose until the administration of the first blinded crossover dose, the day of booster dose or censoring (due to early termination, death, study completion, major protocol deviation, unblinding, data cutoff), whichever is earlier.

As of the data cutoff date, there were a total of 94 first episode cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 (with onset from at least 7 days after second vaccination) accrued in the Per-Protocol efficacy (PP-EFF) Analysis Set in the Initial Vaccination Period. Of these, 18 (all mild) were in the NVX-CoV2373 group and 76 (64 mild, 8 moderate, and 4 severe) were in the placebo group. The resulting vaccine efficacy (VE) of NVX-CoV2373 was estimated as 89.55%, 95% CI (82.54%, 93.75%) based on a Poisson regression model. The study success criterion for the primary efficacy objective was met, as the lower bound (LB) of the 95% CI for VE was >30%, and the point estimate of VE was >50%. In the PP-EFF Analysis Set during the Initial Vaccination Period, there were 12 cases of moderate or severe COVID-19, all of which were in the placebo group. The resulting VE against moderate or severe COVID-19 was 100.00% (95% CI: 84.14%, 100.00%). This analysis also met the success criterion for this endpoint. The effectiveness of the booster dose was inferred based on immunogenicity endpoints and testing for noninferiority of the immune response at 28 days after the booster dose, compared to that at 14 days after the second dose of the primary series. The geometric mean titer ratio (GMTR) of neutralizing antibody response against the ancestral Wuhan strain was 3.2, 95% CI (2.7, 3.8). The respective SCR difference was -1.8%, 95% CI (-6.1%, 2.3%). Thus, the booster immunogenicity success criteria were met and noninferiority was demonstrated, as the GMTR point estimate was >0.83, the LB of the GMTR 95% CI was >0.67, and the LB of the 95% CI of the SCR difference was >-10%.

During the Initial Vaccination Period, the median follow-up time was 3.2 months (range 0 – 20 months). Unsolicited treatment emergent adverse events (TEAEs) within 28 days after the second vaccination were reported at similar frequencies between the NVX-CoV2373 and placebo arms (34.5% and 34.8%, respectively). The most frequently reported unsolicited TEAEs for NVX-CoV2373 and placebo recipients were of the System Organ Class (SOC) of Nervous System Disorders (15.9% versus 17.3%, mainly under the preferred term (PT) of headache [15.1% versus 16.4%]), Respiratory, Thoracic, and Mediastinal Disorders (14.8% versus 15.3%), General Disorders and Administration Site Conditions (11.1% versus 11.4%), Gastrointestinal Disorders (8.6% versus 9.5%), Musculoskeletal and connective tissue disorders (6.7% versus 7.3%), and Infections and Infestations (2.4% and 2.5%). Related (as per the investigator) unsolicited TEAEs within 28 days of the second vaccination were reported more frequently in the NVX-CoV2373 group than in the placebo group (2.4% vs 1.4%, respectively). During the Initial Vaccination Period, serious adverse events (SAEs) were reported for 228 (1.2%) subjects in the NVX-CoV2373 group and for 115 (1.2%) subjects in the placebo group. SAEs were assessed as related to study intervention by the investigator for 6 (< 0.1%) subjects in the NVX-CoV2373 group and for 3 (< 0.1%) subjects in the placebo group. Eighteen participants (11 NVX-CoV2373 and 7 placebo) died during the Initial Vaccination Period. None of the deaths were assessed as related to the study intervention by the investigator, except for one death in the placebo group.

During the Crossover Period, the median follow-up time was 9 months (range 0 – 16 months). Unsolicited TEAEs were reported at a higher frequency after receipt of NVX-CoV2373 (48.1%) than after receipt of placebo (24.4%) within 28 days of the second

vaccination, with a higher frequency of related TEAEs reported also for the NVX-CoV2373 recipients (2.0% vs 0.4%). Note that reactogenicity events were not collected as solicited during the Crossover Period, and thus were captured as unsolicited events for that period. These are also reflected in the higher rates reported among the participants who received NVX-CoV2373, as the vaccine is reactogenic. Severe TEAEs within 28 days of the second vaccination were reported more frequently for the NVX-CoV2373 recipients (16.0%versus 4.9%). The most frequently reported unsolicited TEAEs for the NVX-CoV2373 and placebo recipients, respectively, were of the SOCs of General Disorders and Administration Site Conditions (33.9% and 9.0%), Nervous System Disorders (26.8% and 10.8%), Respiratory, Thoracic, and Mediastinal Disorders (15.3% and 10.6%), Musculoskeletal and Connective Tissue Disorders (26.0% and 5.4%), and Gastrointestinal Disorders (12.3% and 6.4%). Forty participants (10 who received NVX-CoV2373 and 30 who received placebo) died during the Crossover Period, however, none of the deaths in NVX-CoV2373 recipients were considered to be related to vaccination by the investigator. SAEs were reported for 164 (2.6%) NVX-CoV2373 recipients and for 364 (2.4%) placebo recipients. Note that the participants who received placebo during the Crossover Period were subjected to a potential carryover effect as a result of their vaccination with NVX-CoV2373 in the Initial Vaccination Period. Therefore, comparisons between the two groups in the Crossover Period should be interpreted with caution. Further, the Initial and the Crossover Periods had different lengths of follow-up, and therefore comparisons of frequencies between these two periods may be inappropriate.

During the Booster Period, the median follow-up time was 6.7 months (range 0 – 8 months) after vaccination with a booster dose. Unsolicited TEAEs through 28 days after the booster dose of NVX-CoV2373 were reported for 14.3%. Severe TEAEs were reported for 327 (2.4%) participants. SAEs were reported for 227 (1.7%) participants, with 6 (< 0.1%) reporting treatment-related SAEs. One subject experienced a Guillain-Barre syndrome approximately 3 months after receiving a booster dose, however, it was assessed as not related to study intervention by the investigator. Ten (< 0.1%) participants died during the booster period, however, none of these were considered to be related to vaccination by the investigator. Throughout the study, a total of 4 subjects experienced myocarditis, pericarditis, or myopericarditis. Of these, two subjects (<0.1%) reported myocarditis after vaccination with NVX-CoV2373 (on Day 11 after Dose 1, and on Day 29 after Dose 1, respectively). One subject (<0.1%) experienced myopericarditis at 73 days after the second dose of placebo in the initial vaccination period. Two subjects reported pericarditis (one on Day 29 after Dose 1 of NVX-CoV2373 [together with myocarditis], and one on Day 505 after Dose 2 of NVX-CoV2373, respectively).

Solicited local reactions (pain at the injection site, tenderness, redness, and swelling) with onset within 7 days after Dose 1 were reported by 57.9% of the participants in the NVX-CoV2373 group and by 21.2% of the participants in the placebo group. The respective reactions after Dose 2 were reported by 74.6% and by 20.5% of the participants in the NVX-CoV2373 and placebo groups. After the booster dose, these were reported by 72.8%. Pain/tenderness at the injection site was the most commonly reported reaction after NVX-CoV2373 (57.7% after Dose 1, 74.4% after Dose 2, and 72.4% after booster).

Solicited systemic reactions (fever, nausea, vomiting, headache, fatigue, malaise, muscle pain, and joint pain) with onset within 7 days after Dose 1 were reported by 48.2% of the participants in the NVX-CoV2373 group and by 40.8% of the participants in the placebo group. After Dose 2, 69.0% of the participants in the NVX-CoV2373 group and 35.5% of the participants in the placebo group reported at least one systemic reaction. After the booster dose, 69.5% of the participants reported at least one systemic event. The most commonly reported systemic events after NVX-CoV2373 were fatigue/malaise (29.9% after Dose 1, 53.8% after Dose 2, and 55.2% after booster), muscle pain (23.3% after Dose 1, 49.9% after Dose 2, and 51.1% after booster) and headache (25.5% after Dose 1, 44.6% after Dose 2, and 44.3% after booster). Overall, the rates of solicited adverse reactions after the second dose were higher than after the first dose, while the rates after the booster dose were, in general, similar to those after the second dose. Grades 3 and 4 solicited adverse reactions occurred more frequently after the booster dose. Please refer to the review by the clinical reviewer (Dr. Charles Line) for details on the safety analyses.

In the Adolescents portion of the study, a total of 2247 subjects were randomized (2:1 ratio) to receive NVXCoV2373 (N=1491) or placebo (N=756). Of these, 1487 received at least 1 dose of NVXCoV2373 and 745 received placebo pre-crossover (Initial Vaccination Period). During the Crossover Period, a total of 666 subjects received at least 1 dose of NVX-CoV2373, and a total of 1354 subjects received only placebo. A total of 1499 participants received a booster dose of NVX-CoV2373 and were included in the Booster Safety Analysis Set. The effectiveness of NVX-CoV-2373 in adolescents was assessed based on an immunobridging strategy that included testing for noninferiority of the immune response following vaccination with two doses (primary series) of NVX-CoV-2373 in adolescents compared to the immune response following vaccination with two doses of NVX-CoV-2373 in young adults (18 -< 26 years of age) from the Adults portion of study 2019nCoV-301. Accordingly, the Day 35 MN assay neutralizing antibody GMTR against the original Wuhan serotype (SARS-CoV-2 S Wild-Type Virus) was 1.5, 95% CI (1.3, 1.7). The SCR difference was -0.3%, 95% CI (-1.9%, 1.2%). Thus, the study success criteria for the primary immunogenicity objective for immunobridging in adolescents were met, as the LB of the 95% CI for the GMTR was >0.67, the point estimate of GMTR was >0.82, and the LB of the 95% CI for the SCR difference was >-10%.

As of the data cutoff date of August 6, 2022, in the descriptive analysis of efficacy in adolescents, there were a total of 20 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after the second vaccination accrued in the PP-EFF Analysis Set during the Initial Vaccination Period. Of these cases, 6 were in the NVX-CoV2373 group and 14 were in the placebo group. In the NVX-CoV2373 group, all 6 cases were mild in severity, while in the placebo group, 13 cases were mild and 1 was moderate. The resulting VE of NVX-CoV2373 against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination was estimated as 79.82% (95% CI: 47.55%, 92.24%).

The effectiveness of the booster dose in adolescents was inferred based on immunogenicity endpoints and testing for noninferiority of the immune response at 28 days after the booster dose, compared to that at 14 days after the second dose of the primary series in 56 subjects in the Booster PP-IMM Analysis Set. The respectiveneutralizing antibody response (MN50) GMTR against the ancestral Wuhan strain was 2.8, 95% CI (2.1, 3.8). The respective SCR difference was 0, 95% CI (-6.4%, 6.4%). Thus, the booster immunogenicity success criteria were met and noninferiority was demonstrated, as the GMTR point estimate was >0.83, the LB of the GMTR 95% CI was >0.67, and the LB of the 95% CI of the SCR difference was >-10%.

During the Initial Vaccination Period, the rates of unsolicited AEs were similar between the two groups (16.1% versus 16.6%). The most frequently reported unsolicited AEs within 49 days of the first vaccination were of the SOC of Infections and Infestations - by 62 (4.2%) subjects who received NVX-CoV2373, and by 41 (5.5%) subjects who received placebo. Lymphadenopathy was reported more frequently for NVX-CoV2373 recipients (n=11 [0.7%]) than placebo recipients (n=0). Unsolicited AEs that were assessed as related by the investigator were reported for 44 (3.0%) subjects who received NVX-CoV2373 and for 9 (1.2%) subjects who received placebo. Most unsolicited AEs were mild or moderate in severity, with 0.5% of NVX-CoV2373 recipients and 0.8% of placebo recipients experiencing severe AEs. SAEs were reported by 7 (0.5%) subjects who received NVX-CoV2373, and by 2 (0.3%) subjects who received placebo. There were no SAEs that were assessed as related to the study product by the investigator. The median follow-up duration for the Initial Vaccination Period was 2.3 months (range 0.1 - 14.2 months).

During the Crossover Vaccination Period in adolescents, unsolicited AEs were reported by 163 (24.5%) subjects who crossed over to NVX-CoV2373 from placebo and by 242 (17.9%) subjects crossed over from NVX-CoV2373 to placebo. The most frequently reported unsolicited AEs within 49 days of the first crossover vaccination were of the SOC of General disorders and administration site conditions - by 76 (11.4%) subjects who crossed over to NVX-CoV2373, and by 49 (3.6%) subjects who crossed over to placebo. The most frequent among these were Pyrexia (in 5.3% vs 1.1%) and chills (in 4.2% vs 1.1%). Unsolicited AEs that were assessed as related by the investigator were reported for 48 (7.2%) subjects who crossed over to NVX-CoV2373 and for 17 (1.3%) subjects who crossed over to placebo. SAEs were reported by 8 (1.2%) subjects who crossed over to NVX-CoV2373, and by 11 (0.8%) subjects who crossed over to placebo. SAEs that were assessed as related by the investigator were reported only for 1 (0.2%) subject who crossed over to NVX-CoV2373. This was an SAE of myocarditis, which occurred on Day 3 in a male subject (15 years of age) after the second dose of NVX-CoV2373. The median follow-up time after the NVX-CoV2373 vaccine during the Crossover Vaccination Period was 7.7 months (range 1.2 - 11.2 months).

During the Booster Period in adolescents, unsolicited AEs were reported by 96 (6.4%) subjects who received a booster dose of NVX-CoV2373. The most frequently reported unsolicited AEs through 28 days after the booster dose were of the SOC of Infections and Infestations and of Respiratory, thoracic, and mediastinal disorders - by 30 (2.0%)

subjects each. Unsolicited AEs that were assessed as related by the investigator were reported by 17 (1.1%) subjects. SAEs were reported by 19 (1.3%) subjects, but none of these were assessed as related by the investigator. The median follow-up time after the NVX-CoV2373 vaccine during the Booster Vaccination Period was 6.6 months (range 0.7 – 7.3 months). There were no deaths observed in the study in adolescents as of the data cutoff date.

The applicant conducted integrated summary of safety analyses for the primary series, homologous booster dose and heterologous booster dose in adults. Overall, these results were consistent with those from the pivotal study 2019nCoV-301 Adults. Please refer to the review by the clinical reviewer for further details and conclusions on safety.

The statistical methods used by the applicant were generally appropriate and consistent with those prespecified in the study protocol and in the Statistical Analysis Plan (SAP). The main results were verified based on data submitted in the SDTM format.

In conclusion, the primary efficacy objective for the Adults portion of the study was met and the safety profile of the NVX-CoV-2373 vaccine as of the data cutoff date was presented. The safety analyses were descriptive in nature and the study was not powered for formal hypothesis testing between the study arms with regard to safety. I defer to the clinical reviewer whether the observed numerical imbalance for myocarditis and/or pericarditis, and for cardiomyopathy related safety events between the study arms is of clinical significance and whether further investigation for these events in the post-marketing setting is to be recommended. The study demonstrated that the NVX-CoV-2373 vaccine (administered as a two dose [21 days apart] primary series regimen) is efficacious against the primary efficacy endpoint of mild, moderate or severe COVID-19 in adults 18 years of age or older. The effectiveness of a booster dose, administered at least 5 months after the second dose, was inferred based on demonstrating noninferior immune response at 28 days after the booster compared to that at 14 days after the second dose of the primary series. The effectiveness of the primary series of NVX-CoV-2373 vaccine (administered as a two dose [21 days apart] primary series regimen) in adolescents was inferred based on an immunobridging strategy. Specifically, it was demonstrated that the immune response at 14 days after the second dose of NVX-CoV-2373 in adolescents was noninfereior to that in young adults (18 -< 26 years of age) from the Adults portion of study 2019nCoV-301. The effectiveness of a booster dose in adolescents, administered at least 6 months after the second dose, was inferred based on demonstrating noninferiority of the immune response at 28 days after the booster compared to the immune response at 14 days after the second dose of the primary series. No specific safety patterns for adolescents were identified in addition to the reactogenicity events. The effectiveness of the strain-updated vaccine and of the single dose regimen are inferred based on the results of studies 2019nCoV-311 and 2019nCoV-313. Please refer to the review by Dr. Kumaresh Dhara for specific details and conclusions for these studies.

2. Clinical and Regulatory Background

The Novavax COVID-19 Vaccine, Adjuvanted is an adjuvanted recombinant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein nanoparticle vaccine (SARS-CoV-2 rS). The original, Wuhan strain-based vaccine (NVX-CoV2373) was updated for the 2023 – 2024 season to a monovalent Omicron XBB.1.5 subvariant vaccine, and for the 2024-2025 season to a monovalent Omicron JN.1 strain vaccine. The vaccine contains Matrix-M adjuvant.

On July 13, 2022, FDA first authorized the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) under emergency use authorization (EUA) as a 2-dose series of 5 µg recombinant spike protein and 50 µg of Matrix-M adjuvant administered 3 weeks apart for individuals 18 years of age and older. On August 19, 2022, the EUA was amended to include use of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) as a 2-dose series in individuals 12 through 17 years of age. On October 19, 2022, FDA amended the EUA to include use of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) as a single dose, six months after the last COVID-19 Vaccine, in individuals 18 years of age and older for whom an FDA-authorized messenger ribonucleic acid (mRNA) bivalent COVID-19 booster vaccine was not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) because they would otherwise not receive a dose of a COVID-19 vaccine.

On August 30, 2024, the Food and Drug Administration amended the emergency use authorization (EUA) of Novavax COVID-19 Vaccine, Adjuvanted to include the 2024-2025 formula.

3. Submission Quality and Good Clinical Practices

Deficiencies related to the data standards format in the initial submission of the datasets were identified by the data standards reviewer. Updated datasets were submitted to STN 125817/0.33 on August 29, 2024. The datasets were further updated based on Information Requests (IRs) from the data standards reviewer. Updated SDTM datasets were submitted to STN 125817/0.58 on December 30, 2024, and the respective ADaM datasets were submitted to STN 125817/0.62 on January 9, 2025. These submissions resolved the issues related to the format of the datasets. Please refer to the review memo by the data standards reviewer for details. The final submission quality is acceptable.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to the reviews by the corresponding discipline reviewers.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The BLA includes clinical data from the following studies: 2019nCoV-301 (Wuhan formulation - Adults Main Pivotal Study and Adolescents Expansion Pivotal Study), 2019nCoV-311 (Part 1 – Omicron BA.1, Wuhan, BA.1+Wuhan formulations; Part 2 - Omicron BA.5, Wuhan, BA.5+Wuhan formulations), 2019nCoV-101 (Part 1 and Part 2 - Wuhan formulation), 2019nCoV-313 (Omicron XBB.1.5), 2019nCoV-302 (Wuhan formulation), 2019nCoV-501 (Wuhan formulation), 2019nCoV-307 (Wuhan formulation).

The drug substance (SARS-CoV-2 rS) was produced at both (b) (4) (Emergent Manufacturing Operations, Baltimore, Maryland) and (b) (4) (Fujifilm Diosynth Biotechnologies, Research Triangle Park, North Carolina and Serum Institute of India, Pune, India) scales. The (b) (4) scale substance is considered to be consistent with commercial product. The (b) (4) scale produced by Fujifilm Diosynth Biotechnologies was administered as primary series and booster vaccination in Clinical Study 2019nCoV-301 (Adult Main Study and Pediatric Expansion), as single-dose administration in Clinical Study 2019nCoV-307, and during the booster vaccination period in Clinical Studies 2019nCoV-101 (Part 2) and 2019nCoV-501. The drug substance produced at the (b) (4) scale at Serum Institute of India was administered as booster vaccination in Part 1 and Part 2 of Clinical Study 2019nCoV-311. Drug substance produced at the (b) (4) scale was administered as primary series vaccination in Clinical Studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-302, and 2019nCoV-501. The (b) (4) scale product is considered to be different from the (b) (4) scale. Please refer to the review by the CMC reviewer for details.

This review focuses primarily on the efficacy and safety data from the pivotal phase 3 study 2019nCoV-301 (Wuhan formulation - Adults Main Pivotal Study and Adolescents Expansion Pivotal Study). Integrated Summary of Safety (ISS) based on studies 2019nCoV-301, 2019nCoV-311 (Part 1 and Part 2), 2019nCoV-307, 2019nCoV-101 (Part 1, Part 2), 2019nCoV-302, and 2019nCoV-501, is discussed as well as supportive evidence of safety. Studies 2019nCoV-101, 2019nCoV-302, 2019nCoV-501 and 2019nCoV-307 are considered for supportive evidence only as part of the ISS.

For statistical review of clinical studies 2019nCoV-311 and 2019nCoV-313, please refer to the review memo by Dr. Kumaresh Dhara.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The first roll of the BLA was submitted in STN 125817/0.0 (January 31, 2024) and provided the clinical data from studies 2019nCoV-101 and 2019nCoV-307. The second roll was submitted in STN 125817/0.2 (February 29, 2024) and provided the clinical data from studies 2019nCoV-501, 2019nCoV-302 and 2019nCoV-311 Part 2. The third roll was submitted in STN 125817/0.4 (April 1, 2024) and provided the clinical data from

studies 2019nCoV-301, 2019nCoV-311 Part 1, and the ISS. STN 125817/0.15 provided the clinical data up to Day 189 for study 2019nCoV-311 Part 2.

Updated datasets were submitted to STN 125817/0.33 on August 29, 2024.
The datasets were updated further based on IRs from the data standards reviewer. Updated SDTM datasets for study 2019nCoV-301 (adults 17M Addendum, adolescents 12M Addendum, adolescents booster 6M Addendum) were submitted to STN 125817/0.58 on December 30, 2024, and the respective ADaM datasets were submitted to STN 125817/0.62 on January 9, 2025. Updated CSR addendums were submitted to STN 125817/0.64 on January 24, 2025. STN 125817/0.62 contains also updated datasets for studies 2019nCoV-101, 2019nCoV-302, 2019nCoV-311, 2019nCoV-501. The updated PI was submitted to STN 125817/0.108 on January 24, 2025.

In addition to the aforementioned submissions, I have reviewed amendments STN 125817/0.54, 56, 57, 101.

This review memo presents the results from the ISS based on the datasets submitted in STN 125817/0.33. The subsequent changes to the datasets for the individual studies resulted in minor changes in the numbers of subjects with reported unsolicited AEs, as a result of the removal of the events with a preferred term (PT) of "COVID-19" from the AE dataset and the addition of asymptomatic Covid-19 infections as unsolicited AEs (PT of "Asymptomatic COVID-19"). This did not alter the conclusions of the ISS analyses.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the studies that were submitted to STN 125817/0. Study 2019nCoV-301 serves as the primary evidence of safety and effectiveness of the primary series regimen and the booster regimen of NVX-CoV2373 (Original Wuhan formulation) in adults and adolescents. Study 2019nCoV-311 provides evidence of safety and immunogenicity of the SARS-CoV-2 subvariant based formulation, and study 2019nCoV-313 provides evidence of the safety and immunogenicity of the single dose indication. The rest of the studies are included in the ISS as supportive evidence of safety of NVX-CoV2373.

This review focuses primarily on the efficacy and safety data from the pivotal phase 3 study 2019nCoV-301 (Wuhan formulation - Adults Main Pivotal Study and Adolescents Expansion Pivotal Study). The ISS is discussed as well as supportive evidence of safety.

For statistical review of clinical studies 2019nCoV-311 and 2019nCoV-313, please refer to the review memo by Dr. Kumaresh Dhara.

Table 1. Summary of Clinical Studies

Study Number (Status) Countries	**Phase/Study Design**	**Test Product (Dose)**	**Number of Subjects (Randomized)**	**Type of Subjects (Age)**

Study Number (Status) Countries	**Phase/Study Design**	**Test Product (Dose)**	**Number of Subjects (Randomized)**	**Type of Subjects (Age)**
2019nCoV-301 Adult Main Study (ongoing) USA, Mexico Initiated: December 27, 2020 Data Cutoff Date: August 18, 2022	Phase 3, multinational, multicenter, randomized (2:1), observer-blinded, placebo-controlled, crossover study to evaluate the efficacy, safety, and immunogenicity of NVXCoV2373 in adults with a Booster Dose Amendment for the evaluation of a booster dose of NVX-CoV2373.	NVX-CoV2373 (5 µg, Original Wuhan formulation) Primary series: 2 doses 21 days apart Booster dose of NVX-CoV2373: at least 6 months after primary series	Primary series NVX-CoV2373: N=19961 Primary series Placebo: N=9982 Booster NVX-CoV2373: N=13353	Adults ≥ 18 years of age
2019nCoV-301 Pediatric Expansion (ongoing) USA Initiated: April 26, 2021 Data Cutoff Date: August 6, 2022	Phase 3, Pediatric Expansion to the Main Study - multicenter, randomized (2:1), observer-blinded, placebo-controlled, crossover study to evaluate the efficacy, safety, and immunogenicity of NVXCoV2373 in adolescents with a Booster Dose Amendment for the evaluation of a booster dose of NVX-CoV2373.	NVX-CoV2373 (5 µg, Original Wuhan formulation) Primary series: 2 doses 21 days apart Booster dose of NVX-CoV2373: at least 5 months after primary series	Primary series NVX-CoV2373: N=1491 Primary series Placebo: N=756 Booster NVX-CoV2373: N= 1499	Adolescents 12 to < 18 years of age
2019nCoV-311 Part 1 (completed) Australia Initiated: May 31, 2022 Completion Date: October 18, 2023	Phase 3 randomized, observer-blind study of the safety and immunogenicity of a single booster dose of NVX-CoV2515 (Omicron BA.1) and NVX-CoV2373 (Original Wuhan) alone and bivalent prototype and Omicron subvariant vaccine (NVX-CoV2373 + NVX-CoV2515) in previously vaccinated adults.	NVX-CoV2515 (5 µg, Omicron BA.1) NVX-CoV2373 (5 µg, Original Wuhan) NVX-CoV2373 + NVX-CoV2515 (5 µg: Original Wuhan/ BA.1) Bivalent Vaccine	NVX-CoV2515: N=340; NVX-CoV2373: N=335; NVX-CoV2373 + NVX-CoV2515: N=278;	Adults ≥ 18 and ≤ 64 years who have received 2 or 3 doses of the Moderna and/or Pfizer-BioNTech COVID-19 prototype mRNA vaccines ≥ 90 days before study vaccination.

Study Number (Status) Countries	**Phase/Study Design**	**Test Product (Dose)**	**Number of Subjects (Randomized)**	**Type of Subjects (Age)**
2019nCoV-311 Part 2 (ongoing) Australia Initiated: March 22, 2023 Data Cutoff Date: May 31, 2023	Phase 3 randomized, observer-blind study evaluating the safety and immunogenicity of 2 booster doses (Day 0 and Day 90) of NVX-CoV2540 (Omicron BA.5) and NVX-CoV2373 Original Wuhan) alone and bivalent NVX-CoV2373 + NVX-CoV2540 (Original Wuhan/BA.5) vaccine in previously vaccinated adults ≥ 18 years of age.	NVX-CoV2540 (5 µg, Omicron BA.5) NVX-CoV2373 (5 µg, Original Wuhan) NVX-CoV2373 + NVX-CoV2540 (5 µg, Original Wuhan/BA.5) Bivalent Vaccine	NVX-CoV2540: N=255; NVX-CoV2373: N=252; NVX-CoV2373 + NVX-CoV2540: N=259;	Adults ≥ 18 years of age who had received a regimen of ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously.
2019nCoV-313 (Part 1) USA Initiated: September 7, 2023 Data Cutoff Date: October 16, 2023	Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant) in adult participants ≥ 18 years of age previously vaccinated with an mRNA COVID-19 vaccine.	1 booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant)	NVX-CoV2601: N=332	Adults ≥ 18 years of age, previously vaccinated with an mRNA COVID-19 vaccine
2019nCoV-313 (Part 2) (completed) USA Initiated: September 18, 2023 Completion Date: May 20, 2024	Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant) in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve adult participants ≥ 18 years of age.	1 dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant)	NVX-CoV2601: N=338	Adults ≥ 18 years of age, baseline SARS-CoV-2 seropositive, COVID-19 vaccine naïve
2019nCoV-307 (completed) USA Initiated: July 11, 2022 Completion date: August 24, 2022	Phase 3, randomized, observer-blinded, lot-to-lot consistency immunogenicity and safety study in previously vaccinated, medically stable adults, 18 to 49 years of age.	3 different manufacturing lots of NVX-CoV2373 (5 µg, Original Wuhan)	NVX-CoV2373: N=911	Previously vaccinated, medically stable adults, 18 to 49 years of age.

Study Number (Status) Countries	**Phase/Study Design**	**Test Product (Dose)**	**Number of Subjects (Randomized)**	**Type of Subjects (Age)**
2019nCoV-101 Part 1 (completed) Australia Initiated: May 6, 2020 Completion date: June 26, 2021	Phase 1, randomized, observer-blinded, placebo-controlled study of the safety and immunogenicity of NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation) with or without Matrix-M adjuvant (50 µg) in healthy adults (18 to 59 years of age), with no history of SARS-CoV-2 infection or COVID-19.	NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation)	NVX-CoV2373 (5 µg with Matrix-M adjuvant [50 µg] - (b) (4) scale formulation): N=29 Placebo: N=25	Healthy adults, 18 to 59 years of age, with no history of SARS-CoV-2 infection or COVID-19
2019nCoV-101 Part 2 (ongoing) USA, Australia Initiated: August 24, 2020 Data cutoff date: June 1, 2022	Phase 2, randomized, observer-blinded, placebo-controlled study of the safety and immunogenicity of 4 dose regimens of NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation) with Matrix-M adjuvant (50 µg) and of 6- and 12-month booster regimens in healthy adults (18 to 84 years of age), with no history of SARS-CoV-2 infection or COVID-19 resulting in medical intervention (mild COVID-19 was allowed)	NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation)	NVX-CoV2373: N=514 Placebo: N=255	Healthy adults (18 to 84 years of age), with no history of SARS-CoV-2 infection or COVID-19 resulting in medical intervention (mild COVID-19 was allowed)
2019nCoV-302 (completed) United Kingdom Initiated: September 28, 2020 Completion date: March 29, 2022	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of NVX-CoV2373 ((b) (4) scale formulation) in healthy and clinically stable adults (18 to 84 years of age) in the United Kingdom (UK).	NVX-CoV2373 (b) (4) (b) (4 scale formulation)	NVX-CoV2373: N=7592 Placebo: N=7593	Healthy and clinically stable adults, 18 to 84 years of age in the UK
2019nCoV-501 (completed) South Africa Initiated: August 17, 2020 Completion	Phase 2, randomized, observer-blinded, placebo-controlled efficacy, safety and immunogenicity study of NVX-CoV2373 ((b) (4) scale formulation) in healthy HIV-negative adults 18 to 84 years of age and medically stable	NVX-CoV2373 (b) (4) (b) (4 scale formulation)	NVX-CoV2373: N=2213 Placebo: N=2206	Healthy HIV-negative adults 18 to 84 years of age and medically stable PLWH 18 to 64 years of age, with negative PCR test result

Study Number (Status) Countries	Phase/Study Design	Test Product (Dose)	Number of Subjects (Randomized)	Type of Subjects (Age)
date: August 13, 2021	people living with human immunodeficiency virus (PLWH) 18 to 64 years of age, with negative PCR test result within 5 days prior to first vaccination.			within 5 days prior to first vaccination

Source: Created by the reviewer based on the Clinical Study Reports submitted to STN 125817/0.

5.4 Consultations

5.4.1 Advisory Committee Meeting

Please refer to the review memos of EUA 28237 for information on the Advisory Committee Meetings that were held to discuss the investigational product. There was no advisory committee meeting for this original BLA.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 2019nCoV-301 Adults

This section discusses the 2019nCoV-301 Adults Main study. For discussions on the 2019nCoV-301 Pediatric Expansion in adolescents study, please refer to Section 6.2.

Study 2019nCoV-301 Adults Main Pivotal Study is a phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled, crossover study to evaluate the efficacy, safety, and immunogenicity of NVXCoV2373 (Original Wuhan formulation SARS-CoV-2 rS [5 µg] + Matrix-M1 adjuvant [50 µg]) in adults ≥ 18 years of age, with a Booster Dose Amendment for the evaluation of a booster dose of NVX-CoV2373. The study also includes a Pediatric Expansion in adolescent participants 12 to < 18 years of age (see Section 6.2).

The study was conducted in the United States (U.S.) and Mexico.

6.1.1 Objectives

Table 2. Study 2019nCoV-301 Adults Objectives and Endpoints

Objectives:	Endpoints:
Primary Objective:	**Primary Endpoint:**

Objectives:	**Endpoints:**
To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age.	First episode of PCR-positive mild, moderate, or severe COVID-19, where severity is defined as: **Mild COVID-19 (≥ 1 of the following):** • 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 o or difficulty breathing compared to baseline. o New onset fatigue. o New onset 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. **OR Moderate COVID-19 (≥ 1 of the following):** • High fever (≥ 38.4 °C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days). • Any evidence of significant LRTI: 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 (ie, crackles/rales, wheeze, rhonchi, pleural rub, stridor).

Objectives:	**Endpoints:**
	OR Severe COVID-19 (≥ 1 of the following): • Tachypnea: ≥ 30 breaths per minute at rest. • Resting heart rate ≥ 125 beats per minute. • SpO2: ≤ 93% on room air or PaO2/FiO_2 < 300 mmHg. • High flow O_2 therapy or NIV/NIPPV (ie, CPAP or BiPAP). • Mechanical ventilation or ECMO. • One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following: o Acute respiratory failure, including ARDS. o Acute renal failure. o Acute hepatic failure. o Acute right or left heart failure. o Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg). 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.
Key Secondary Objective:	**Key Secondary Endpoint**
• To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant not considered as a "variant of concern / interest" according to the CDC Variants Classification, diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age.	• First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern/interest" according to the CDC Variants Classification.
Other Secondary Objectives:	**Other Secondary Endpoints:**
• To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second vaccination in the initial set of vaccinations of adult participants ≥ 18 years of age. • To assess VE against ANY symptomatic SARS-CoV-2 infection.	• First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint. • ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab and ≥ 1 of any of the following symptoms: o Fever. o New onset cough. o New onset or worsening of shortness of breath or difficulty breathing compared to baseline.

Objectives:	**Endpoints:**
• To assess VE according to race and ethnicity. • To assess VE in high-risk adults versus non-high-risk adults (high-risk is defined by age ≥ 65 years with or without co-morbidities or age < 65 years **with** co-morbidities [e.g., obesity (BMI > 30 kg/m^2), chronic kidney or lung disease, cardiovascular disease and diabetes mellitus type 2] and/or by life circumstance [living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances (e.g., factory or meat packing plants, essential retail workers, etc.)]). • To assess the durability of VE (measured by all defined efficacy endpoints) in initial active vaccine recipients versus crossover (delayed) active vaccine recipients.[1] • To describe the humoral immune response to vaccine in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population Participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti-NP antibodies at baseline. • To assess the immune response to vaccine by IgG antibody to SARS-CoV-2 S protein and hACE2 inhibiting antibodies at Day 35 and later for all Immunogenicity Population participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable anti-NP antibodies at baseline. • To assess the durability of immune response (IgG antibody to SARS-CoV-2 S protein, hACE2 inhibition, and MN) pre-booster vaccine dose and at 18 and 24 months of study in all Immunogenicity Population participants, and for subsets with and without detectable anti-NP antibodies at baseline or prior to crossover set of vaccinations.[1] • To describe and compare the safety experience for the vaccine versus placebo in adult participants ≥ 18 years of age based on solicited short-term reactogenicity by toxicity grade for 7 days following each vaccination (Days 0 and 21) after the initial set of vaccinations. • To assess overall safety through 49 days (28 days after second injection of each set of vaccinations [initial and crossover]) and to compare vaccine versus placebo for all unsolicited AEs and MAAEs. • To assess the frequency and severity of MAAEs attributed to vaccine, AESIs, or SAEs through the EoS and to compare vaccine versus placebo after each set of vaccinations (initial and crossover).	○ New onset fatigue. ○ New onset generalized muscle or body aches. ○ New onset headache. ○ New loss of taste or smell. ○ Acute onset of sore throat, congestion or runny nose. ○ New onset nausea, vomiting or diarrhea. • Neutralizing antibody titers from Immunogenicity Population at Days 0, 35, immediately prior to administration of the crossover set of vaccinations and at specified time points through EoS. • Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers from Immunogenicity Population at Days 0, 35, immediately prior to administration of the crossover set of vaccinations and at specified time points through EoS. • Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form. • Reactogenicity incidence and severity (mild, moderate or severe) recorded by all participants on their eDiary on days of vaccination and subsequent 6 days (total 7 days after each vaccine injection in the initial set of vaccinations). • Reactogenicity endpoints include injection site reactions: ○ Pain. ○ Tenderness. ○ Erythema. ○ Swelling/induration. And systemic reactions: ○ Fever. ○ Malaise. ○ Fatigue. ○ Arthralgia. ○ Myalgia. ○ Headache. ○ Nausea/vomiting. • Incidence and severity of MAAEs through 49 days, i.e., 28 days after second injection of each set of vaccinations (initial and crossover). • Incidence and severity of unsolicited AEs through 49 days, i.e., 28 days after second injection of each set of vaccinations (initial and crossover). • Incidence and severity of SAEs, MAAEs attributed to trial vaccine and AESIs at specified time points until Month 24 or the EoS.

Objectives:	**Endpoints:**
• To assess all-cause mortality in vaccine versus placebo recipients after each set of vaccinations (initial and crossover). • To describe the severity and course of COVID-19 in vaccine versus placebo recipients in terms of healthcare requirements, utilization and medical assessments after each set of vaccinations (initial and crossover).[1] • To assess the proportion of participants (vaccine versus placebo recipients) with SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, including specifically undiagnosed infection, across the 2 years of study follow-up. • To assess the VE against SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, regardless of whether the infection was symptomatic. • To assess in a subset of participants the immunogenicity of a new lot of SARS-CoV-2 rS with Matrix-M adjuvant in comparison to the lot utilized in the initial set of vaccinations (i.e., immunobridging).	• Death due to any cause. • Data points to be collected for healthcare requirements, utilization and medical assessments from participants who become ill on study will be defined in a separate substudy protocol. • Antibodies to SARS-CoV-2 NP at Days 0 and 35, immediately prior to administration of the crossover set of vaccinations, and at specified timepoints until Month 24 will be used to determine natural infection and to determine the incidence of undiagnosed infection acquired during study follow-up. • Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic. • IgG antibodies to SARS-CoV-2 rS at approximately 35 days after the first crossover vaccination in approximately 300 active vaccine recipients 18 to ≤ 64 years of age enrolled at selected study sites.
Post-Booster Objectives:	**Post-Booster Endpoints:**

Objectives:	**Endpoints:**
• To assess the incidence of PCR-confirmed symptomatic COVID-19 (as defined above) following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) in adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) in adult participants. • To assess the incidence of PCR-confirmed symptomatic COVID-19 due to a SARS-CoV-2 variant not considered as a "variant of concern/interest" according to the CDC Variants Classification following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants.[1] • To assess the incidence of PCR-confirmed symptomatic COVID-19 due to a SARS-CoV-2 variant considered as a "variant of concern/ interest" according to the CDC Variants Classification following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants.[1] • To assess the incidence of PCR-confirmed moderate-to-severe symptomatic COVID-19 (as defined above) following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active	• First episode of PCR-positive mild, moderate, or severe COVID-19 (as defined above) occurring ≥ 7 days after the booster vaccine dose. • First episode of PCR-positive COVID-19 (as defined above) occurring ≥ 7 days after the booster vaccine dose and shown by gene sequencing to represent a variant not considered as a "variant of concern/interest" according to the CDC Variants Classification.[1] • First episode of PCR-positive COVID-19 (as defined above) occurring ≥ 7 days after the booster vaccine dose and shown by gene sequencing to represent a "variant of concern/interest" according to the CDC Variants Classification.[1] • First episode of PCR-positive moderate-to-severe COVID-19 (as defined above) occurring ≥ 7 days after the third(booster) vaccine dose.[1] • Neutralizing antibody titers, serum levels of IgG to SARS-CoV-2 S protein and hACE2 inhibition titers from Immunogenicity Population immediately prior and at 28 days after administration of the booster vaccine dose. • Positive anti-NP antibody titers at any pre-specified time point following the booster vaccine dose in participants with no intervening symptoms of COVID-19.[1] • Immune response after the booster vaccine dose by neutralizing antibody titer and IgG antibody to SARS-CoV-2 rS protein and by hACE2 inhibition titers at prespecified time points through EoS in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies.[1] • PCR-confirmed SARS-CoV-2 infection detected in participants without symptoms of COVID-19

Objectives:	**Endpoints:**
vaccination (initial or crossover series) for adult participants.[1] • To assess the incidence of any PCR-confirmed symptomatic or moderate-to-severe symptomatic COVID-19 (as defined above) following a third(booster) vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants.[1] • To assess the incidence of development of anti-NP antibodies following a booster vaccine dose among participants without intervening symptomatic COVID-19.[1] • To describe the humoral immune response at 28 days after the booster vaccine dose in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population Participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable pre-booster vaccine dose anti-NP antibodies. • To assess the immune response at 28 days after the booster vaccine dose by IgG antibody to SARS-CoV-2 S protein and hACE2 inhibition titers in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies. • To assess the durability of immune response after the booster vaccine dose by neutralizing antibody titer and IgG antibody to SARS-CoV-2 rS protein and by hACE2 inhibition titers at prespecified timepoints through EoS in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies.[1] • To assess the level of humoral immune response following the booster vaccine dose in comparison to that after completion of the initial active Novavax vaccinations series. • To describe the safety experience for the vaccine in adult participants based on solicited short-term reactogenicity by toxicity grade for 7 days following the booster vaccine dose. • To assess overall safety through 28 days after the booster vaccine dose.	illness based on NP swabs obtained at prespecified time points after booster injections.[1] • Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case occurring ≥ 7 days after the booster vaccine dose via the Endpoint Form.[1] • Reactogenicity (as defined above) incidence and severity (mild, moderate, or severe) recorded by all participants on their eDiary on day of the booster vaccination and subsequent 6 days. • Incidence and severity of unsolicited AEs through 28 days after the booster vaccine dose. • Incidence and severity of MAAEs attributed to trial vaccine, SAEs and AESIs through EoS. • Death due to any cause.

Objectives:	Endpoints:
• To assess the frequency and severity of MAAEs attributed to vaccine, AESIs, or SAEs through EoS. • To assess all-cause mortality after a booster vaccine dose. • To contribute to a larger cross-study NIH effort to define correlates of risk and protection against SARS-CoV-2 infection and disease following a booster vaccine dose.[1]	

Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bilevel positive airway pressure; BMI = body mass index; CPAP = continuous positive airway pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; FiO2 = fraction of inspired oxygen; hACE2 = human angiotensin-converting enzyme 2; ICU = intensive care unit; IgG = immunoglobulin G; IL = interleukin; LRTI = lower respiratory tract infection; MN = microneutralization; NIH = National Institutes of Health; NP = nucleocapsid; NIPPV = noninvasive positive pressure ventilation; NIV = non-invasive ventilation; O2 = oxygen; PaO2 = partial pressure of oxygen; PCR = polymerase chain reaction; PE = pulmonary embolism; SBP = systolic blood pressure; SpO2 = oxygen saturation; VE = vaccine efficacy.
1. Objectives/endpoints not addressed in this interim report due to incompleteness or as yet unavailable data are noted in the table; this includes immunogenicity data and data from the period after blinded crossover.
Source: Adapted from the 2019nCoV-301 Adults 17 Month Clinical Study Report, dated July 11, 2023, Table 3, p. 41 (STN 125817/0/4).

6.1.2 Design Overview

In the Adult Main Study, in the Initial Vaccination Period, approximately 30,000 adults were planned to be randomized in a 2:1 ratio (stratified by age - 18 to < 65 years and ≥ 65 years) to receive a primary series of 2 doses (21 days apart) of NVX-CoV2373 or placebo (saline), as shown in Table 3. According to the protocol, priority for enrollment was to be given to individuals at high risk for COVID-19. Eligible participants were to be medically stable with no history of previous laboratory-confirmed (by PCR or serology to SARS-CoV-2) diagnosis of SARS-CoV-2 infection or COVID-19 prior to randomization. In the blinded crossover period (approximately 2 months after completion of the primary series), participants were planned to receive 2 injections of the alternate product (21 days apart) in a blinded manner. Participants were to be offered to receive a single dose of NVX-CoV2373 at least 6 months after completion of active vaccination in the Booster Vaccination Period.

Solicited Adverse Reactions (local and systemic reactogenicity) were planned to be collected via eDiary for 7 days after each dose during the Initial Vaccination Period. Unsolicited AEs and MAAEs were to be collected for 49 days (i.e., 28 days after second injection of the initial and crossover series). Follow-up for MAAEs, AESIs, SAEs was to be conducted through study completion.

The study includes surveillance for COVID-19 as part of the assessment of the efficacy endpoints. Participants were planned to be provided with a thermometer and instructed to monitor daily their body temperature throughout the study and to record temperature and other symptoms in their eDiary. When a same symptom was reported for at least 2

consecutive days, participants were to be directed (via the eDiary) to begin daily nasal self-swabbing for PCR testing at home for 3 days or until the participant experiences 2 consecutive asymptomatic days. Participants were to be instructed at their enrollment on the methods of nasal self-swabbing for COVID-19 and the completion of the FLU-PRO symptom reporting instrument. FLU-PRO instrument and the prompts for self-swabbing are not included in the post-booster phase. The eDiary would alert the study site to contact the participant to schedule an in-person Acute Illness Visit. During the first 4 days after the second vaccination or the booster vaccine dose in the Booster Amendment, when solicited systemic reactogenicity symptoms may be similar to those of COVID-19, investigators were to use their clinical judgement to decide if an Acute Illness visit was warranted. Active surveillance for COVID-19 was planned to continue through the end of study (EoS). The self-swabs were to be shipped to the central laboratory (at the University of Washington, Seattle, WA). At the in-person Acute Illness Visit, participants were planned to undergo a physical examination as well as a medically attended nasal swab and a blood sample for serologic testing. The medically attended swabs were to be shipped to the central laboratory as well. Participants whose nasal swabs (home or medically attended) are confirmed at the central lab to be PCR-positive for SARS-CoV-2, would be scheduled for a Convalescent Visit. The Convalescent Visit was planned to occur approximately 1 month after the onset of the PCR-confirmed case of COVID-19 to assess status of AEs, record the clinical course of the disease on the Endpoint Assessment Form, and to obtain a blood sample for convalescent serologic testing. Participants who reported a positive test for COVID-19 outside the study would be asked to complete a convalescent visit to record the timing and severity of COVID-19 infection. These cases would not be included in the primary endpoint cases.

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) were planned to be collected from all participants before the first vaccination and at selected subsequent time points, including prior to the crossover set of vaccinations. Testing was planned to be performed on a subset of collected sera from the Immunogenicity Population of up to ~1,200 participants (randomly selected). Blood samples were planned to be obtained at 14 days after the second crossover vaccination dose from ~900 participants 18 to ≤ 64 years of age.

Table 3. Study Design for 2019nCoV-301 Adults

Arm	Planned Sample Size	Initial Vaccination Period	Crossover Vaccination Period	Booster Vaccination Period
-	-	2 doses (21 days apart)	2 doses (21 days apart)	1 dose (≥ 6 m. after an active Primary Series)
NVXCoV2373	N up to 20,000: 18 - 64 years: ≤ 15,000 65+ years: ≥ 5,000	NVXCoV2373	Placebo	NVXCoV2373
Placebo	N up to 10,000 18 - 64 years: ≤ 7,000 65+ years: ≥ 2,500	Placebo	NVXCoV2373	NVXCoV2373

Note: NVXCoV2373 refers to Intramuscular (IM) injection of the Original Wuhan formulation SARS-CoV-2 rS [5 µg] + Matrix-M1 adjuvant [50 µg]; Placebo refers to IM injection of normal saline.

Source: Created by the reviewer based on the 2019nCoV-301 Clinical Study Protocol, Version 13.0, dated December 15, 2022, submitted to STN 125817/0.

6.1.3 Population

The study included adults ≥18 years of age who were considered to be at risk of exposure and infection with SARS-CoV-2, and who were medically stable with no history of previous laboratory-confirmed (by PCR or serology to SARS-CoV-2) diagnosis of SARS-CoV-2 infection or COVID-19. The study was conducted at sites in the U.S. and Mexico.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- NVXCoV2373 - Original Wuhan formulation of SARS-CoV-2 rS (5 μg) + Matrix-M1 adjuvant (50 μg), administered as an Intramuscular (IM) injection.
- Placebo – normal saline, administered as an IM injection.

6.1.6 Sites and Centers

The study was conducted at 119 sites (113 in the U.S. and 6 in Mexico).

6.1.8 Hypotheses and Criteria for Study Success

Primary Efficacy Objective:

$$H_0: VE \leq 30\% \text{ vs } H_a: VE > 30\%;$$

where VE is defined as the percentage relative risk (RR) reduction between the 2 groups in the incidence of the primary efficacy endpoint of PCR-confirmed symptomatic mild, moderate or severe COVID-19 illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations, i.e. VE (%) = (1 – RR) x 100. The Primary analysis will be performed based on the data generated prior to the blinded crossover and the PP-EFF analysis set. The success criteria were that the lower bound (LB) of the 95% CI is >30% and the point estimate of VE is ≥ 50%. One analysis was planned for assessment of the primary objective.

Noninferiority Booster Immunogenicity Objective:

$$H_{01}: GMT_{booster} / GMT_{D35} \leq 0.67 \text{ vs } H_{a1}: GMT_{booster} / GMT_{D35} > 0.67,$$

$$H_{02}: SCR_{booster} - SCR_{D35} \leq -10\% \text{ vs } H_{a2}: SCR_{booster} - SCR_{D35} > -10\%,$$

where $GMT_{booster}$ refers to the MN_{50} geometric mean titers (GMTs) against SARS-CoV-2 Wild-Type virus (Ancestral Wuhan Strain) at 28 days after a single booster dose, and GMT_{D35} refers to the respective MN_{50} GMTs at Day 35, i.e., 14 days after dose 2 in the initial set of vaccinations. $SCR_{booster}$ and SCR_{D35} refer to the respective seroconversion rates (SCRs) in MN_{50} against SARS-CoV-2 Wild-Type virus. Seroconversion is defined on the subject level as having ≥ 4-fold increase from baseline if the baseline value is above or equal to the assay's lower limit of quantification (LLOQ) or having a post-baseline value ≥ 4 times the LLOQ if the baseline is below the assay's LLOQ. Seroconversion rate (SCR) is the percentage of subjects achieving seroconversion. For

$SCR_{booster}$ estimation, baseline is the value measured on the day of the booster dose prior to vaccination.

Upon success of the primary efficacy objective, the Noninferiority Booster Immunogenicity Objective was to be assessed. Success would be achieved if the LB of the 95% CI of the GMR = $GMT_{booster}$ / GMT_{D35} is > 0.67, the point estimate of the GMR is > 0.83, and the LB of the 95% CI of $SCR_{booster}$ - SCR_{D35} is >-10%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for study 2019nCoV-301 Adults (version 13, dated December 15, 2022) was submitted with the application in STN 125817/0. A brief overview of the SAP is presented below.

Analysis populations: The definitions of the study Analysis Populations are shown in Table 4. The primary population for efficacy analyses was the PP-EFF Population. The primary population for the immunogenicity booster objective was the Booster PP-IMM Analysis Set.

Table 4. Analysis Populations

Population	Description
Intent-to-Treat (ITT) Analysis Set	All participants who were randomized. Participants were to be analyzed according to the treatment arm they were randomized.
Full Analysis Set (FAS)	All participants who were randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. The FAS population were to be analyzed according to the treatment group to which they were randomized.
Safety Analysis Set	All participants who received at least 1 dose of trial vaccine. Participants in the safety analysis set were to be analyzed according to the vaccine actually received. If a participant received both active and placebo, the participant was to be analyzed as part of the active group.
Per-Protocol Efficacy (PP-EFF) Analysis Set	All participants who received the full prescribed initial regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 PCR-positive episode (i.e., participants were 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 was to enroll 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 serology, were excluded from the PP-EFF population. PP-EFF were the primary set for analysis of efficacy endpoints for the pre-crossover period.

Population	Description
Per-Protocol Efficacy 2 (PP-EFF-2) Analysis Set	Included the same population as in the PP-EFF analysis set, with the exception that it included participants regardless of baseline SARS-CoV-2 serostatus.
Per-Protocol Immunogenicity (PP-IMM) Analysis Set	The PP-IMM analysis set were determined for each study visit. The PP-IMM analysis set included participants that had at least a baseline and 1 serum sample result available after vaccination and had no major protocol violations that were considered clinically relevant to impact immunological measures at the visit in question. The PP-IMM analysis set also excluded participants who had a PCR positive nasal swab between baseline up to the visit analyzed. For visits on or after Day 21, participants must have received the second vaccination to be included in the PP-IMM analysis set.
Per-Protocol Immunogenicity 2 (PP-IMM-2) Analysis Set	Included the same population as in the PP-IMM analysis set, with the exception that it included participants regardless of baseline status SARS-CoV-2 serostatus.
Booster Safety Analysis Set	All participants in the safety analysis set who received a dose during the booster portion of the study.
Booster PP-IMM Analysis Set	Included subjects who received 2 doses of the active vaccine either in the initial vaccination period or in the blinded crossover vaccination period, had a blood sample collected at the day of the first active dose, at Day 35 after the primary series, did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose, did not receive an emergency use authorized COVID-19 vaccine, received the booster dose, did not unblind, and did not have major protocol deviations through 7 days post-crossover Dose 2.

Source: Created by the reviewer based on the information provided in 2019nCoV-301 Statistical Analysis Plan, Version 10.0, dated April 10, 2023, submitted to STN 125817/0.

Analysis for the Primary, Key Secondary and Other Secondary Efficacy Endpoints:

Primary Analysis

The primary efficacy endpoint was derived based on the investigator assessments (including severity and start date) collected in the Endpoint Assessment CRF and were based on PCR test results from the central lab of the University of Washington (Section 6.1.2) in the Initial Vaccination Period. The primary efficacy endpoint was assessed as the first occurrence of mild, moderate or severe PCR-positive COVID-19 during the period of 7 days after the second vaccine dose until the blinded crossover, the day of booster dose or censoring (due to early termination, death, study completion, major protocol deviation, unblinding, data cutoff), whichever was earlier.

The primary analysis population for the efficacy analyses was the PP-EFF Analysis Set. The VE was defined as VE (%) = (1 – RR) x 100, where RR = relative risk of incidence rates between the 2 study arms (NVXCoV2373/Placebo). The RR were estimated by exponentiating the treatment group coefficient from a Poisson regression model with robust error variance (as per Zou, 2004). To account for differences in follow-up times starting at 7 days after the second vaccination, an offset was used in the Poisson regression model. The age stratum was included as a covariate. A two-sided, 95% CI

were derived based on the Poisson regression analysis to assess the study success criteria (Section 6.1.8).

For the analyses of primary and key secondary endpoints, a gatekeeping testing strategy was planned to be applied by requiring a successful rejection of the null hypothesis for the primary endpoint, before testing the key secondary endpoint using the same success criterion at a one-sided alpha of 0.025. Additionally, sequential testing strategy was planned upon success on the key secondary endpoint to be conducted for the secondary endpoints of moderate-to-severe COVID-19, followed by assessment of VE against mild, moderate or severe COVID-19 in the subgroup of non-high risk adults, and then in the subgroup of high risk adults. The null hypothesis to be assessed for these secondary endpoints was H_0:VE ≤ 0%.

Analysis for the Booster Immunogenicity Endpoints:
Primary Analysis
The booster immunogenicity endpoints were assessed in the Booster PP-IMM Analysis Set. The 95% CIs for GMT and GMFR were calculated based on the t-distribution of the log-transformed values, and then back transformed to the original scale. The 95% CIs for the SCRs were based on the Clopper-Pearson method. The comparison between the SCRs were based on the Tango method. The noninferiority success criteria were assessed according to Section 6.1.8.

Analyses for the Safety Endpoints:
Safety endpoints were summarized by vaccine group according to the study intervention that the participants actually received (Safety Analysis Set). The proportion of participants reporting each safety endpoint and the respective 95% CI based on the Clopper-Pearson method were reported. The 95% CI for the difference in the proportions (between study groups) were based on the Miettinen and Nurminen method.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The data cut-off date for the study results that were submitted to the BLA is August 18, 2022. The study was initiated on December 27, 2020. There were 29943 subjects who were randomized to receive NVXCoV2373 (N=19961) or placebo (N=9982) (Table 5). Of the randomized participants, 29582 (98.8%) were vaccinated with at least 1 dose, and 28527 (95.3%) were vaccinated with 2 doses. A larger percentage of subjects in the placebo arm (27.4%) discontinued during the Initial vaccination period compared to the NVXCoV2373 arm (15.7%). The majority of the discontinuations were after the second dose (n=2567 [12.9%] in the NVXCoV2373 arm, and n=2345 [23.5%] in the placebo arm). The main reason for discontinuation was due to withdrawal by the participant. The blinded crossover vaccination period started on April 20, 2021. A total of 15319 (76.7%) subjects from the NVX-CoV2373 arm and a total of 6395 (64.1%) subjects from the placebo arm received at least one dose of the alternate product during the blinded crossover period. The disproportionate percentage of subjects receiving a dose in the crossover period was due to the higher proportion of subjects in the placebo arm who

discontinued during the Initial vaccination period. The booster vaccination period was initiated on December 20, 2021. A total of 13,353 (44.6%) participants received a booster dose of NVX-CoV2373.

Overall, as of the data cutoff date, none of the subjects had completed the study, and 7702 (38.6%) in the NVXCoV2373 arm and 4384 (43.9%) in the placebo arm have discontinued the study. A slightly higher % of participants in the placebo arm have discontinued. One reason for this was the disproportionately higher percentage of subjects in the placebo arm who were unblinded prematurely in order to receive an EUA-approved COVID-19 vaccine.

Table 5. Disposition of Participants (as Randomized)

Population	**NVXCoV2373 N[1]=19961 n (%)**	**Placebo N[1]=9982 n (%)**	**Total N[1]=29943 n (%)**
Initial Vaccination Period:	-	-	-
Completed at least 1 dose	19714 (98.8)	9868 (98.9)	29582 (98.8%)
Completed 2 doses	19087 (95.6)	9440 (94.6)	28527 (95.3)
Discontinued from initial vaccination period	3128 (15.7)	2731 (27.4)	5859 (19.6)
Reason for discontinuation:	-	-	-
Withdrawal by participant	1955 (9.8)	1866 (18.7)	3821 (12.8)
Lost to follow-up	1008 (5.0)	730 (7.3)	1738 (5.8)
Other	134 (0.7)	121 (1.2)	255 (0.9)
Adverse event	20 (0.1)	6 (< 0.1)	26 (< 0.1)
Death	11 (< 0.1)	8 (< 0.1)	19 (< 0.1)
Crossover Period:	-	-	-
Completed dose 3	15319 (76.7)	6395 (64.1)	21714 (72.5)
Completed dose 4	15104 (75.7)	6328 (63.4)	21432 (71.6)
Discontinued during the crossover vaccination period	3768 (18.9)	1320 (13.2)	5088 (17.0)
Reason for discontinuation:	-	-	-
Withdrawal by participant	2152 (10.8)	665 (6.7)	2817 (9.4)
Lost to follow-up	1434 (7.2)	573 (5.7)	2007 (6.7)
Other	148 (0.7)	68 (0.7)	216 (0.7)
Death	30 (0.2)	10 (0.1)	40 (0.1)
Adverse event	4 (< 0.1)	4 (< 0.1)	8 (< 0.1)
Booster Period:	-	-	-
Received a booster dose[2]	9181 (46.0)	4172 (41.8)	13353 (44.6)
Discontinued on/after booster	703 (3.5)	256 (2.6)	959 (3.2)
Reason for discontinuation:	-	-	-
Lost to follow-up	413 (2.1)	166 (1.7)	579 (1.9)
Withdrawal by participant	246 (1.2)	76 (0.8)	322 (1.1)
Other	34 (0.2)	10 (0.1)	44 (0.1)
Death	9 (< 0.1)	3 (< 0.1)	12 (< 0.1)

Population	NVXCoV2373 N[1]=19961 n (%)	Placebo N[1]=9982 n (%)	Total N[1]=29943 n (%)
Adverse event	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Overall:	-	-	-
Completed	0	0	0
Ongoing[3]	12259 (61.4)	5598 (56.1)	17857 (59.6)
Discontinued	7702 (38.6)	4384 (43.9)	12086 (40.4)
Reason for discontinuation:	-	-	-
Withdrawal by participant	4385 (22.0)	2618 (26.2)	7003 (23.4)
Lost to follow-up	2891 (14.5)	1515 (15.2)	4406 (14.7)
Other	350 (1.8)	219 (2.2)	569 (1.9)
Death	51 (0.3)	21 (0.2)	72 (0.2)
Adverse event	25 (0.1)	11 (0.1)	36 (0.1)
Trial vaccine blind broken by site	3472 (17.4)	2496 (25.0)	5968 (19.9)
Reason for unblinding:	-	-	-
Unblinded with the intention to receive EUA vaccine	3472 (17.4)	2496 (25.0)	5968 (19.9)
Other reasons	0	0	0

[1] Denominator in the respective group.
[2] Both arms received NVXCoV2373 as a booster dose.
[3] As of the data cutoff date (August 18, 2022).
Source: Created by the reviewer based on the submitted data and the information provided in 2019nCoV-301 Adult 17-Month Clinical Study Report, eSub 3 CSR Addendum, dated January 18, 2025, submitted to STN 125817/0/64.

For the initial vaccination period (i.e., the earliest of early termination, death, first crossover dose, booster dose, or data cutoff), the median follow-up time after the first dose was 3.2 months (range 0-20), and the median follow-up after the second dose was 2.5 months (range 0-19), and 3089 (10.4%) subjects have completed at least 6 months of follow-up during that period. Of the vaccinated subjects, 27545 (93.1%) subjects had completed at least 1 month of follow-up after dose 2.

Table 6 shows the analysis populations (see Table 4 for the definitions). The Safety Population included a total of 19735 participants who have received at least one dose of NVX-CoV2373 and 9868 participants who have received placebo during the Initial Vaccination Period. The PP-EFF analysis population included 17184 subjects in the NVX-CoV2373 arm and 8326 subjects in the placebo arm. The most frequent reason for exclusion from the PP-EFF analysis population was due to a baseline positive anti-NP result (5.8%). A total of 13,353 participants received a booster dose of NVX-CoV2373 and were included in the Booster Safety Analysis Set. Of the 298 participants who were sampled from the Booster Safety Analysis Set for inclusion in the Booster PP-IMM Analysis Set, 225 participants were included.

Table 6. Analysis Populations

Analysis Sets	**NVX-CoV2373 N = 19961 n (%)**	**Placebo N = 9982 n (%)**	**Total N = 29943 n (%)**
ITT	19961 (100)	9982 (100)	29943 (100)
Excluded from All Following Analysis Sets:	-	-	-
Applicant Exclusion[1]	195 (1.0)	94 (0.9)	289 (1.0)
Not dosed	52 (0.3)	20 (0.2)	72 (0.2)
FAS	19714 (98.8)	9868 (98.9)	29582 (98.8)
Safety Analysis Set[2]	19735	9847	29582
PP-EFF	17184 (86.1)	8326 (83.4)	25510 (85.2)
Excluded:[3]	2777 (13.9)	1656 (16.6)	4433 (14.8)
Baseline positive anti-NP result	1100 (5.5)	622 (6.2)	1722 (5.8)
Censored prior to observation period	742 (3.7)	*466* (4.7)	*1208* (4.0)
Protocol deviation	289 (1.4)	252 (2.5)	541 (1.8)
Unblinded	339 (1.7)	195 (2.0)	534 (1.8)
Post-baseline positive PCR results	*114* (0.6)	*80 (0.8)*	*194 (0.6)*
End of follow-up	*68 (0.3)*	*62 (0.6)*	*130 (0.4)*
Death	0	1 (< 0.1)	1 (< 0.1)
Did not complete vaccination schedule	627 (3.1)	428 (4.3)	1055 (3.5)
Baseline positive PCR result	229 (1.1)	109 (1.1)	338 (1.1)
PP-EFF-2	18348 (91.9)	8974 (89.9)	27322 (91.2)
PP-IMM Day 35	2095 (10.5)	948 (9.5)	3043 (10.2)
Excluded:[3]	17866 (89.5)	9034 (90.5)	26900 (89.8)
Sample not collected (Baseline or Subsequent Visit)	17455 (87.4)	8798 (88.1)	26253 (87.7)
Baseline positive anti-NP result	1100 (5.5)	622 (6.2)	1722 (5.8)
Did not complete vaccination schedule	631 (3.2)	456 (4.6)	1087 (3.6)
Baseline positive PCR results	229 (1.1)	109 (1.1)	338 (1.1)
Protocol deviation	26 (0.1)	39 (0.4)	65 (0.2)
Infection prior to visit	15 (< 0.1)	9 (< 0.1)	24 (< 0.1)
PP-IMM-2 Day 35	2219 (11.1)	1022 (10.2)	3241 (10.8)
Booster Safety Set[4]	9181 (46.0)	4172 (41.8)	13353 (44.6)
Booster PP-IMM[4]	113 (0.6)	112 (1.1)	225 (2.7)

[1] The applicant excluded all participants from Site US151 due to source data inadequate to verify clinical data and other Good Clinical Practice violations, and some participants from Site US076 who received NVX-CoV2373 from single-dose vials (the same material evaluated in earlier trials, (b) (4) formulation), rather than the multi-dose vials evaluated in this study.
[2] The safety analysis set is based on actual treatment received, rather than assigned treatment, therefore percentages are not presented.
[3] Includes the Applicant Exclusion and those who were not dosed. Note that subjects may meet more than one exclusion criteria.

[4] All subjects in this set received NVX-CoV2373 as a booster dose during the booster period.
Source: Created by the reviewer based on the submitted data and the information provided in 2019nCoV-301 Addendum 1.0 to Adult 17-Month Clinical Study Report, dated March 12, 2024, submitted to STN 125817/0/4.

6.1.10.1.1 Demographics

Table 7 shows the demographic and baseline characteristics by study group for the Safety Population. The characteristics were comparable between the study groups. For the PP-EFF Analysis Set, the demographic and baseline characteristics were distributed similarly and were also comparable between the two study arms.

Table 7. Demographic and Baseline Characteristics (Safety Population)

Characteristic	NVX-CoV2373 N = 19735	Placebo N = 9847	Total N = 29582
Age (years)	-	-	-
Mean (SD)	46.5 (15.05)	46.8 (14.95)	46.6 (15.02)
Median (range)	47.0 (18, 95)	47.0 (18, 90)	47.0 (18, 95)
Age group, n (%)	-	-	-
18 to < 65 years	17255 (87.4)	8612 (87.5)	25867 (87.4)
≥ 65 years	2480 (12.6)	1235 (12.5)	3715 (12.6)
Sex, n(%)	-	-	-
Male	10367 (52.5)	5019 (51.0)	15386 (52.0)
Female	9368 (47.5)	4828 (49.0)	14196 (48.0)
Race, n (%)	-	-	-
White	14795 (75.0)	7381 (75.0)	22176 (75.0)
Black or African American	2322 (11.8)	1164 (11.8)	3486 (11.8)
American Indian or Alaska Native[1]	1309 (6.6)	660 (6.7)	1969 (6.7)
Asian	809 (4.1)	416 (4.2)	1225 (4.1)
Multiple	326 (1.7)	160 (1.6)	486 (1.6)
Native Hawaiian or Other Pacific Islander	56 (0.3)	12 (0.1)	68 (0.2)
Not Reported	110 (0.6)	47 (0.5)	157 (0.5)
Missing	8 (< 0.1)	7 (< 0.1)	15 (< 0.1)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	4333 (22.0)	2155 (21.9)	6488 (21.9)
Not Hispanic or Latino	15346 (77.8)	7669 (77.9)	23015 (77.8)
Not Reported	32 (0.2)	19 (0.2)	51 (0.2)
Unknown	22 (0.1)	3 (< 0.1)	25 (< 0.1)
Missing	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
BMI (kg/m^2) category, n (%)	-	-	-
Underweight (< 18.0 kg/m^2)	134 (0.7)	59 (0.6)	193 (0.7)
Normal (18.0 – 24.9 kg/m^2)	5740 (29.1)	2832 (28.8)	8572 (29.0)
Overweight (25.0 – 29.9 kg/m^2)	6359 (32.2)	3187 (32.4)	9546 (32.3)

Characteristic	NVX-CoV2373 N = 19735	Placebo N = 9847	Total N = 29582
Obese (≥ 30.0 kg/m^2)	7402 (37.5)	3729 (37.9)	11131 (37.6)
Missing	100 (0.5)	40 (0.4)	140 (0.5)
Occupation, n (%)	-	-	-
Currently working	13454 (68.2)	6705 (68.1)	20159 (68.1)
Working in close proximity to others	7796 (39.5)	3798 (38.6)	11594 (39.2)
Student attending school in person	1132 (5.7)	518 (5.3)	1650 (5.6)
In-person schooling/currently working/ working in close proximity to others, n (%)	13849 (70.2)	6906 (70.1)	20755 (70.2)
Days/week at workplace, n (%)	-	-	-
0 days/week	3055 (15.5)	1610 (16.4)	4665 (15.8)
1 day/week	955 (4.8)	447 (4.5)	1402 (4.7)
2 – 4 days/week	3411 (17.3)	1728 (17.5)	5139 (17.4)
≥ 5 days/week	6007 (30.4)	2913 (29.6)	8920 (30.2)
PPE used by people at workplace	10265 (52.0)	5074 (51.5)	15339 (51.9)
Living situation, mean (SD)	-	-	-
Number of people living with participant	2.0 (3.65)	1.9 (3.28)	2.0 (3.53)
Number of co-habitants under 18 years	0.6 (1.77)	0.6 (1.38)	0.6 (1.65)
Number of co-habitants 18 to < 65 years	1.2 (2.71)	1.2 (3.01)	1.2 (2.81)
Number of co-habitants ≥ 65 years	0.2 (0.46)	0.2 (0.45)	0.2 (0.46)
Number attending school living with participant	0.5 (1.92)	0.5 (2.93)	0.5 (2.31)
Country, n (%)	-	-	-
U.S.	18559 (94.0)	9259 (94.0)	27818 (94.0)
Mexico	1176 (6.0)	588 (6.0)	1764 (6.0)
High-risk adults[2], n (%)	-	-	-
Yes	18812 (95.3)	9380 (95.3)	28192 (95.3)
No	923 (4.7)	467 (4.7)	1390 (4.7)
Comorbidities, n (%)	-	-	-
Obesity (BMI ≥ 30 kg/m^2)	7287 (36.9)	3667 (37.2)	10954 (37.0)
Chronic lung disease	2796 (14.2)	1455 (14.8)	4251 (14.4)
Diabetes mellitus type 2	1531 (7.8)	817 (8.3)	2348 (7.9)
Cardiovascular disease	230 (1.2)	129 (1.3)	359 (1.2)
Chronic kidney disease	150 (0.8)	68 (0.7)	218 (0.7)
Baseline serostatus, n (%)	-	-	-
Seronegative and PCR negative	18461 (93.5)	9156 (93.0)	27617 (93.4)
Seropositive and PCR positive	1274 (6.5)	691 (7.0)	1965 (6.6)

Abbreviations: BMI = body mass index; eCRF = electronic case report form; PCR = polymerase chain reaction; PPE = personal protective equipment; SD = standard deviation.
1. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were American Indians enrolled at sites in the U.S.

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.
Source: Adapted from 2019nCoV-301 Adult 17-Month Clinical Study Report, eSub 3 CSR Addendum, dated January 18, 2025, submitted to STN 125817/0/64, Table 9, p. 25.

Of note, subjects from site MX-007 as well as those subjects who did not have PCR/Anti-NP results available at baseline were assumed Negative at baseline for the demographics analysis. They were also not excluded from PP-EFF.

6.1.11 Efficacy Analyses

The application included data and results based on the data cutoff date of August 18, 2022.

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy endpoint was derived based on the investigator assessments (severity and start date) collected in the Endpoint Assessment CRF and was based on PCR test results from the Central Laboratory at the University of Washington (Section 6.1.2) during the Initial Vaccination Period. The primary efficacy endpoint was defined as the first occurrence of mild, moderate or severe PCR-positive COVID-19 starting during the period of 7 days after the second vaccine dose until the administration of the first blinded crossover dose, the day of booster dose or censoring (due to early termination, death, study completion, major protocol deviation, unblinding, data cutoff), whichever was earlier.

The SAP specified that the study would have a single primary efficacy analysis, i.e., no interim analyses would be conducted and the whole alpha level would be spent on the hypothesis testing for the primary efficacy endpoint using all pre-crossover blinded follow-up data. The applicant conducted evaluation of the primary efficacy endpoint based on a data cutoff date of June 1, 2021, however in the study CSR (dated July 11, 2023), they pointed out that there were late arriving data, data revisions and new data from additional follow-up that were not captured in the June 1, 2021 analysis. Therefore, at the time of the subsequent data cutoff date of September 27, 2021, they updated their primary efficacy endpoint analysis. This was the analysis that was included in the applicant's EUA filing. Subsequently, at the time of the data cutoff date of August 18, 2022, further revisions to the data were stated, specifically to the Per-Protocol Analysis Sets and the respective cases. As a result, the applicant updated their primary efficacy analysis to reflect the revised datasets. Note that the differences in the results were minor and there were no differences in the conclusions between the three different datasets.

This review memo discusses the results from the data cutoff date of August 18, 2022, as the respective dataset addressed identified inaccuracies in the datasets from the previous data cutoff dates.

Primary Efficacy Endpoint of Mild, Moderate or Severe COVID-19

A total of 94 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination were accrued in the PP-EFF Analysis Set during the Initial Vaccination Period (Table 8). Of these cases, 18 (0.105%) participants were in the NVX-CoV2373 group and 76 (0.913%) were in the placebo group. In the NVX-CoV2373 group, all 18 cases were mild in severity, while in the placebo group, 64 cases were mild, 8 were moderate, and 4 were severe. The respective VE was 89.55% (95% CI: 82.54%, 93.75%) based on a Poisson regression model.

Table 8. Vaccine Efficacy of NVX-CoV2373 – Mild, Moderate or Severe COVID-19 in the Initial Vaccination Period (PP-EFF Analysis Set)

Parameter	**NVX-CoV2373 N = 17184**	**Placebo N = 8326**	**VE %[2] (95% CI)**
Participants with a primary endpoint case [1], n (%)	18 (0.105)	76 (0.913)	89.55 (82.54, 93.75)
Severity, n (%):	-	-	-
Mild	18 (0.105)	64 (0.769)	-
Moderate	0	8 (0.096)	-
Severe	0	4 (0.048)	-
Median surveillance time (days)	63.0	57.0	-
Mean incidence rate per year in 1000 people, (95% CI)[3]	5.98 (3.74, 9.54)	57.19 (45.67, 71.61)	-

[1] As per the definition in Table 2.
[2] Modified Poisson regression with logarithmic link function, vaccine group and age strata as fixed effects and robust error variance [Zou 2004].
[3] Mean incidence was calculated with weighting for 18 to < 65-year and ≥ 65-year groups reflective of the distribution seen in the study population.
Source: Adapted from 2019nCoV-301 Addendum 1.0 to Adult 17-Month Clinical Study Report, dated March 12, 2024, Table 15, p. 49, submitted to STN 125817/0/4.

Reviewer's comment: The study success criterion for the primary efficacy objective was met, as the LB of the 95% CI for VE was >30%, and the point estimate of VE was >50%.

Supportive analysis using Cox proportional hazard model resulted in a VE of 89.66% (95% CI: 82.72%, 93.82%).

A supportive analysis in the PP-EFF-2 analysis set of the primary efficacy endpoint included 96 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19, with 19 (0.104%; all mild cases) in the NVX-CoV2373 group and 77 (0.858%; 65 mild, 8 moderate, and 4 severe) in the placebo group. The respective VE was 88.94% (95% CI: 81.73%, 93.30%).

Reviewer's comment: The supportive analyses were consistent with the primary efficacy analysis and resulted in the same conclusions.

Table 9 shows descriptive subgroup analyses by demographic and baseline characteristics for the primary efficacy endpoint in the PP-EFF Analysis Set. VE for the 18 to <65 years of age subgroup was 90.78%, (95% CI: 83.92%, 94.72%). For the ≥ 65 years of age subgroup there were very few cases accumulated which resulted in a very wide CI for VE, which precludes drawing conclusions about this age group. VE for the 50 to < 65 years of age was estimated as 89.19%, (95% CI: 67.88%, 96.36%), which is comparable to the overall VE.

Table 9. Subgroup Analyses for Vaccine Efficacy of NVX-CoV2373 – Mild, Moderate or Severe COVID-19 in the Initial Vaccination Period (PP-EFF Analysis Set)

Variables	**NVX-CoV2373 Cases [1]/N (%) (Mean Incidence Rate/1,000 person-years) [2]**	**Placebo Cases [1]/N (%) (Mean Incidence Rate/1,000 person-years) [2]**	**Vaccine Efficacy % [2] (95% CI)**
Age:	-	-	-
18 to < 65 years	15/15162 (0.099) (5.70)	72/7365 (0.978) (61.82)	90.78 (83.92, 94.72)
≥ 65 years	3/2022 (0.148) (8.58)	4/961 (0.416) (26.82)	67.99 (-43.01, 92.83)
50 to < 65 years	4/5525 (0.072) (4.24)	17/2809 (0.605) (39.26)	89.19 (67.88, 96.36)
Sex:	-	-	-
Male	8/8950 (0.089) (5.13)	28/4204 (0.666) (42.27)	87.86 (73.39, 94.46)
Female	10/8234 (0.121) (6.83)	48/4122 (1.164) (71.41)	90.43 (81.09, 95.16)
Race:	-	-	-
White	14/13059 (0.107) (6.32)	57/6311 (0.903) (59.37)	89.35 (80.90, 94.06)
Black or African American	1/1878 (0.053) (2.97)	8/941 (0.850) (49.41)	93.99 (51.92, 99.25)
American Indian or Alaska Native [3]	1/1056 (0.095) (4.37)	6/511 (1.174) (55.58)	92.14 (34.81, 99.05)
Asian	0/750 (0) (0.00)	4/373 (1.072) (69.38)	100.00 (33.48, 100.00) [4]
Native Hawaiian or Other Pacific Islander	0/47 (0) (0.00)	0/10 (0) (0.00)	NE [4]
Multiple	2/295 (0.678) (39.08)	0/136 (0) (0.00)	NE [4]
Ethnicity:	-	-	-
Hispanic or Latino	9/3672 (0.245) (13.05)	18/1782 (1.010) (57.65)	77.36 (49.60, 89.83)
Not Hispanic or Latino	9/13473 (0.067) (3.92)	58/6532 (0.888) (57.82)	93.21 (86.30, 96.64)
Country:	-	-	-
U.S.	17/16187 (0.105) (6.14)	72/7838 (0.919) (59.31)	89.65 (82.45, 93.90)
Mexico	1/997 (0.100) (4.28)	4/488 (0.820) (36.10)	88.14 (-6.00, 98.67)
High-risk condition: [5]	-	-	-

Variables	NVX-CoV2373 Cases [1]/N (%) (Mean Incidence Rate/1,000 person-years) [2]	Placebo Cases [1]/N (%) (Mean Incidence Rate/1,000 person-years) [2]	Vaccine Efficacy %[2] (95% CI)
No	1/811 (0.123) (7.14)	1/405 (0.247) (16.27)	56.14 (-3342.81, 99.44)
Yes	17/16373 (0.104) (5.91)	75/7921 (0.947) (59.09)	90.00 (83.07, 94.09)
Comorbidities: [6]	-	-	-
No	10/9123 (0.110) (6.20)	38/4318 (0.880) (55.37)	88.80 (77.53, 94.41)
Yes	8/8061 (0.099) (5.66)	38/4008 (0.948) (58.51)	90.32 (79.26, 95.49)
Chronic lung disease	1/2474 (0.040) (2.35)	9/1266 (0.711) (45.39)	94.82 (58.62, 99.35)
Cardiovascular disease	1/203 (0.493) (29.23)	2/104 (1.923) (121.97)	76.04 (-360.28, 99.59)
Diabetes	1/1300 (0.077) (4.32)	5/694 (0.720) (43.54)	90.09 16.11, 98.83
BMI > 30	6/6320 (0.095) (5.26)	33/3134 (1.053) (61.61)	91.47 79.63, 96.43
Chronic renal disease	1/123 (0.813) (47.26)	1/60 (1.667) (101.74)	53.55 (-3546.53, 99.41)
Chronic liver disease	1/103 (0.971) (57.66)	0/49 (0) (0.00)	NE
HIV	0/134 (0) (0.00)	1/49 (2.041) (127.35)	100.00 (-1293.97, 100.00)

Abbreviations: NE = Not Estimable.
[1] Primary efficacy endpoint cases as per the definition in Table 2.
[2] Mean incidence rate and RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, vaccine group and age strata as fixed effects and robust error variance [Zou 2004]. By age group summaries included vaccine group only as a fixed effect. Mean incidence was calculated with weighting for 18 to < 65-year and ≥ 65-year groups reflective of the distribution seen in the study population.
[3] 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 U.S.
[4] When there are zero cases in either vaccine group or the total number of cases in both vaccine groups combined is < 5, VE and 95% CI are calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases, adjusted for total surveillance time.
[5] High-risk adults were defined as 1) age ≥ 65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age < 65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.
[6] Comorbidities included obesity (BMI > 30 kg/m2), chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and/or chronic kidney disease.
Source: Adapted from 2019nCoV-301 Addendum 1.0 to Adult 17-Month Clinical Study Report, dated March 12, 2024, Table 15, p. 49, submitted to STN 125817/0/4 and eSub 3 CSR Addendum, dated January 18, 2025, submitted to STN 125817/0/64, Table 13, p. 34.

<u>Reviewer's comment:</u> The VE analyses by subgroups are of limited value in many of the subgroups due to the small numbers of cases accrued. Therefore, these results should be considered descriptive and should be interpreted with caution.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoint of Mild, Moderate or Severe COVID-19 due to a SARS-CoV-2 variant not considered as a "variant of concern"

The key secondary endpoint was specified as a case of first episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern/interest" (VOC/VOI) according to the CDC Variants Classification. Of the 94 primary endpoint cases in the PP-EFF Analysis Set, viral genetic sequences were available for 73 participants. Of these cases, 15 were identified by the applicant as prototype-like that did not contain any of the mutations that would identify them as a VOC (1 [0.006%] in the NVX-CoV2373 group and 14 [0.168%] in the placebo group). The respective VE was 96.85% (95% CI: 76.01%, 99.59%). The applicant stated that the variant classification was based on the June 2021 CDC classification for VOC/VOI and the December 2021 WHO classification for VOC/VOI/VUM (variant under monitoring). The success criterion for this endpoint was met.

Secondary Endpoint of Moderate or Severe COVID-19

Since the primary and key secondary efficacy endpoints met the success criteria, the applicant conducted hypothesis testing for the secondary endpoint of moderate or severe COVID-19. In the PP-EFF Analysis Set during the Initial Vaccination Period, there were 12 cases of moderate or severe COVID-19, of which 0 were in the NVX-CoV2373 group and 12 (0.144%) were in the placebo group. The resulting VE was 100.00% (95% CI: 84.14%, 100.00%). This analysis also met the success criterion for this endpoint.

Booster Immunogenicity Endpoints

The applicant assessed the booster immunogenicity endpoints to test the Booster Noninferiority Hypothesis (see Section 6.1.8). The neutralizing antibody response (MN50) against the ancestral Wuhan strain GMTs at 28 days post booster dose in the Booster PP-IMM Analysis Set was 4947.1, 95% CI (4315.6, 5671.1) compared to GMTs at 14 days post Dose 2 of the primary series of 1553.4, 95% CI (1277.3, 1889.1), as shown in Table 10. The respective GMTR was 3.2, 95% CI (2.7, 3.8). The SCR at 28 days post booster dose (relative to the pre-booster) was 92.3%, 95% CI (88.0%, 95.5%) compared to the SCR at 14 days post Dose 2 of the primary series of 94.1%, 95% CI (90.2%, 96.8%). The respective SCR difference was -1.8%, 95% CI (-6.1%, 2.3%).

Reviewer's comment: The booster immunogenicity success criteria were met, as the GMTR point estimate was >0.83, the LB of the GMTR 95% CI was >0.67, and the LB of the 95% CI of the SCR difference was >-10%. Thus, noninferiority of the immune response after the booster dose compared to after the primary series was demonstrated.

Table. 10. Neutralizing Antibody Response (MN50) Against SARS-CoV-2 Wild-Type Virus (Ancestral Wuhan Strain) in Serologically Negative Adult Participants (Booster PP-IMM Analysis Set)

Parameters	**NVX-CoV2373 Booster N = 222**
Day 0 (Time of 1st dose)	-
Median	10.0
Min - max	10 – 1280
GMT	11.3
95% CI	10.4, 12.2
Day 35 (14 days after 2nd dose)	-
Median	2560.0
Min - max	10 – 40960
GMT	1553.4
95% CI	1277.3, 1889.1
SCR relative to time of 1st dose, n/N (%)	209/222 (94.1)
95% CI	90.2, 96.8
Time of booster	-
Median	80.0
Min - max	10 – 10240
GMT	122.3
95% CI	99.6, 150.2
28 days post-booster	-
Median	5120.0
Min - max	160 – 81920
GMT	4947.1
95% CI	4315.6, 5671.1
SCR relative to time of 1st dose, n/N (%)	219/222 (98.6)
95% CI	96.1, 99.7
Difference in SCRs	4.5
95% CI	2.5, 8.1
GMTR relative to 14 days after 2nd dose	3.2
95% CI	2.7, 3.8
SCR relative to time of booster, n/N (%)	205/222 (92.3)
95% CI	88.0, 95.5
Difference in SCRs	-1.8
95% CI	-6.1, 2.3

Source: Adapted from 2019nCoV-301 Adult 17-Month Clinical Study Report, dated July 11, 2023, Table 92, p. 231, submitted to STN 125817/0/4.

6.1.12 Safety Analyses

This section summarizes the main safety analysis results. The safety analyses were descriptive in nature, and no formal hypothesis testing was planned. For a more detailed discussion of the safety results, please refer to the clinical review memo by Dr. Charles Line.

Unsolicited AEs

Initial Vaccination Periods

A summary of the rates of unsolicited AEs for study participants vaccinated during the Initial Vaccination Period and the Crossover Vaccination Period are shown in Table 11. It should be noted that based on recommendations of the data standards reviewer, these rates include AEs that were collected through the COVID-19 Daily Diary that did not correspond to a COVID-19 event. Asymptomatic COVID-19, COVID-19 pneumonia, and medical history records with a start date after randomization were also counted as unsolicited AEs. Events of COVID-19 and COVID-19 Daily Diary terms that corresponded to a COVID-19 event (comprising the PTs of chills, pyrexia, pain, myalgia, headache, nasal congestion, and rhinorrhoea) were not counted as unsolicited AEs.

The median follow-up duration time during the Initial Vaccination Period was 3.2 months (range 0 – 20 months). The respective frequencies of participants reporting unsolicited treatment emergent AEs (TEAEs) after vaccination were similar between the two arms. Of note, TEAE is defined as any AE occurring or worsening on or after the first dose of trial vaccine. The different AE categories shown in Table 11 were generally comparable between the two arms. The most frequently reported unsolicited TEAEs (≥ 1.5% of in a vaccine group) for NVX-CoV2373 and placebo recipients, respectively, were of the System Organ Class (SOC) of Nervous System Disorders (15.9% versus 17.3%, mainly under the PT of headache [15.1% versus 16.4%]), Respiratory, Thoracic, and Mediastinal Disorders (14.8% versus 15.3%), General Disorders and Administration Site Conditions (11.1% versus 11.4%), Gastrointestinal Disorders (8.6% versus 9.5%), Musculoskeletal and connective tissue disorders (6.7% versus 7.3%), and Infections and Infestations (2.4% and 2.5%). The applicant conducted an analysis of lymphadenopathy within 7 days after vaccination. Lymphadenopathy was reported more frequently for NVX-CoV2373 recipients (0.051% for dose 1 and 0.136% for dose 2) than placebo recipients (0.020% for dose 1 and 0.011% for dose 2), with a higher proportion of NVX-CoV2373 recipients reporting lymphadenopathy following dose 2 than dose 1. Most of these events were mild, and there were no severe events. Related (as per the investigator) unsolicited TEAEs within 28 days of second vaccination were reported more frequently in the NVX-CoV2373 group than in the placebo group (2.4% vs 1.4%, respectively). Most unsolicited TEAEs within 28 days of the second vaccination were mild or moderate in severity.

SAEs were reported for 228 (1.2%) subjects in the NVX-CoV2373 group and for 115 (1.2%) subjects in the placebo group during the initial vaccination period. SAEs were assessed as related by the investigator for 6 (< 0.1%) subjects in the NVX-CoV2373 group and for 3 (< 0.1%) subjects in the placebo group. Among these, there was one event of thrombocytopenia occurring 32 days after the second dose of NVX-CoV2373.

Eighteen participants (11 NVX-CoV2373 and 7 placebo) died during the Initial Vaccination Period. None of the deaths were assessed as related to the study intervention by the investigator, except for one event in the placebo group.

Table 11. Summary of Unsolicited Adverse Events During the Initial and Crossover Vaccination Periods (Safety Analysis Set)

Participants reporting at least one AE	**Initial Period NVX-CoV2373 N = 19735 n (%)**	**Initial Period Placebo N = 9847 n (%)**	**Crossover Period NVX-CoV2373 N = 6416 n (%)**	**Crossover Period Placebo N = 15298 n (%)**	**Booster Period NVX-CoV2373 N = 13353 n (%)**	**Overall after 1st Dose of NVX-CoV2373 N = 26124 n (%)**
Unsolicited TEAEs through 28 days after second vaccination/booster dose	-	-	-	-	-	-
Unsolicited TEAE[1]	6817 (34.5)	3423 (34.8)	3088 (48.1)	3730 (24.4)	1913 (14.3)	-
Related unsolicited TEAE	476 (2.4)	141 (1.4)	129 (2.0)	61 (0.4)	92 (0.7)	-
Severe unsolicited TEAE	1049 (5.3)	562 (5.7)	1026 (16.0)	743 (4.9)	327 (2.4)	-
Related severe unsolicited TEAE	19 (< 0.1)	6 (< 0.1)	5 (< 0.1)	3 (< 0.1)	11 (< 0.1)	-
MAAE	969 (4.9)	476 (4.8)	269 (4.2)	555 (3.6)	334 (2.5)	-
Unsolicited TEAE (without COVID-19 Symptom Daily Diary data)	2323 (11.8)	1087 (11.0)	547 (8.5)	922 (6.0)	633 (4.7)	-
Severe unsolicited TEAE (without COVID-19 Symptom Daily Diary data)	146 (0.7)	63 (0.6)	35 (0.5)	63 (0.4)	44 (0.3)	-
Unsolicited TEAEs through data cut-off date[2]	-	-	-	-	-	-
Any MAAE	1097 (5.6)	530 (5.4)	377 (5.9)	795 (5.2)	501 (3.8)	2452 (9.4)
Related MAAE	102 (0.5)	25 (0.3)	26 (0.4)	29 (0.2)	33 (0.2)	183 (0.7)
SAE	228 (1.2)	115 (1.2)	164 (2.6)	364 (2.4)	227 (1.7)	926 (3.5)
Related SAE	6 (< 0.1)	3 (< 0.1)	2 (< 0.1)	4 (< 0.1)	6 (< 0.1)	18 (<0.1)
AESI (PIMMCs)	27 (0.1)	13 (0.1)	13 (0.2)	19 (0.1)	18 (0.1)	71 (0.3)
Related AESI (PIMMCs)	17 (< 0.1)	3 (< 0.1)	7 (< 0.1)	5 (< 0.1)	2 (< 0.1)	30 (0.1)

Participants reporting at least one AE	Initial Period NVX-CoV2373 N = 19735 n (%)	Initial Period Placebo N = 9847 n (%)	Crossover Period NVX-CoV2373 N = 6416 n (%)	Crossover Period Placebo N = 15298 n (%)	Booster Period NVX-CoV2373 N = 13353 n (%)	Overall after 1st Dose of NVX-CoV2373 N = 26124 n (%)
AESIs relevant to COVID-19	5 (< 0.1)	6 (< 0.1)	5 (< 0.1)	9 (< 0.1)	9 (< 0.1)	28 (0.1)
Related relevant to COVID-19	0	1 (< 0.1)	0	0	0	0
Deaths	11 (< 0.1)	7 (< 0.1)	10 (0.2)	30 (0.2)	10 (< 0.1)	61 (0.2)
TEAE leading to discontinuation of the vaccine	60 (0.3)	21 (0.2)	3 (< 0.1)	15 (< 0.1)	-	77 (0.3)
Related TEAE leading to discontinuation of the vaccine	13 (< 0.1)	3 (< 0.1)	1 (< 0.1)	2 (< 0.1)	-	16 (<0.1)
TEAE leading to study discontinuation	27 (0.1)	11 (0.1)	10 (0.2)	26 (0.2)	11 (< 0.1)	74 (0.3)
Related TEAE leading to study discontinuation	4 (< 0.1)	2 (< 0.1)	0	0	0	4 (<0.1)
Follow-up time Median (range) (months) [2]	3.2 (0 - 20)	3.2 (0 - 20)	9.0 (0 – 16)	9.0 (0 – 16)	6.7 (0 - 8)	15.9 (0 - 20)

Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
[1] Includes COVID-19 Symptom collected through the COVID-19 Daily Diary.
[2] Within the respective vaccination period.
Source: Adapted from eSub3 Addendum to 2019nCoV-301 Adult 17-Month Clinical Study Report, dated January 18, 2025, submitted to STN 125817/0/64, Table 26-27 (p. 53-54), Table 28-29 (p. 55-56), Table 30-31 (p. 57-58); 2019nCoV-301: Adult 17-Month Clinical Study Report, dated July 11, 2023, Tables 111-113 (p. 290-291); Reviewer's computations, based on the submitted datasets.

Crossover Vaccination Periods

The median follow-up time during the blinded Crossover Period was 9 (range 0 - 16) months (Table 11). Unsolicited TEAEs were reported at a higher frequency after receipt of NVX-CoV2373 (48.1%) than after receipt of placebo (24.4%) within 28 days of the second vaccination, with a higher frequency of related TEAEs reported also for the NVX-CoV2373 recipients (2.0% vs 0.4%). Since reactogenicity events were not collected as solicited during the blinded crossover vaccination period, they were reported as unsolicited. Most unsolicited TEAEs reported within 28 days of the second vaccination were mild or moderate in severity, however, severe TEAEs were also reported more frequently for the NVX-CoV2373 recipients within 28 days of the second vaccination (16.0%versus 4.9%). The most frequently reported unsolicited TEAEs (≥ 1.5% in a vaccine group) for the NVX-CoV2373 and placebo recipients, respectively, were of the SOCs of General Disorders and Administration Site Conditions (33.9% and 9.0%), Infections and Infestations (1.6% and 1.5%), Nervous System Disorders (26.8% and

10.8%), Respiratory, Thoracic, and Mediastinal Disorders (15.3% and 10.6%), Musculoskeletal and Connective Tissue Disorders (26.0% and 5.4%), and Gastrointestinal Disorders (12.3% and 6.4%). Forty participants (10 who received NVX-CoV2373 and 30 who received placebo) died during the Crossover Period, and none of the deaths in the NVX-CoV2373 recipients were considered to be related to vaccination by the investigator. SAEs were reported for 164 (2.6%) NVX-CoV2373 recipients and for 364 (2.4%) placebo recipients, with treatment-related SAEs reported for 2 (< 0.1%) NVX-CoV2373 recipients and 4 (< 0.1%) placebo recipients.

A total of 26106 subjects received at least one dose of NVX-CoV2373 as a primary series during the Initial Vaccination Period or during the Crossover Period.

Reviewer's comment: The participants who received placebo during the Crossover Period were potentially subjected to a carryover effect as a result of their vaccination with NVX-CoV2373 in the Initial Vaccination Period. Therefore, comparisons between the two groups in the Crossover Period should be interpreted with caution. Further, the Initial and the Crossover periods had a different length of follow-up, and therefore comparisons between the two periods may be inappropriate. Additionally, reactogenicity events were not collected as solicited during the Crossover Period, and thus were captured as unsolicited events for that period. These are reflected in the higher rates reported among the participants who received NVX-CoV2373 during the Crossover Period, as the vaccine is reactogenic (see Solicited AEs section below).

Booster Vaccination Period
The median follow-up time during the Booster Period was 6.7 (range 0 - 8) months (Table 11). Unsolicited TEAEs through 28 days after the booster dose of NVX-CoV2373 were reported for 14.3%. Most TEAEs (through 28 days after the booster dose) were mild or moderate, with severe TEAEs reported for 327 (2.4%) participants. MAAEs through 28 days after the booster dose were reported for 334 (2.5%) participants. SAEs were reported for 227 (1.7%) participants, with 6 (< 0.1%) participants reporting treatment-related SAEs. Ten (< 0.1%) participants died during the booster period, however none of these were considered to be related to vaccination by the investigator.

One subject experienced Guillain-Barre syndrome approximately 3 months after receiving a booster dose. This event was assessed as not related to study intervention by the investigator. Throughout the study, a total of 6 subjects experienced thrombocytopenia, however, for only 1 subject the event (SAE, 32 days after dose 2 of SARS-CoV-2 vaccine) was assessed as related to vaccination by the investigator.

Through data cutoff, after receipt of first dose of NVX-CoV2373
A total of 26124 subjects received at least 1 dose of NVX-CoV2373. The median follow-up time after receipt of the first dose of NVX-CoV2373 was 15.9 months (range 0 – 20 months), shown in Table 11. Throughout the study, after the receipt of a dose of NVX-CoV2373, there were 21 SAEs in 18 (0.07%) subjects that were assessed as related to study intervention by the investigator. These included SAEs such as tendonitis (n=1), deep vein thrombosis (n=1), pulmonary embolism (n=2), etc. Most of these events

occurred after the second dose of NVX-CoV2373 or after the booster. The median day of onset since the last dose of NVX-CoV2373 was 25 days (range: 2 – 130 days). None of these events resulted in death. A total of 4 subjects experienced myocarditis, pericarditis, or myopericarditis. Of these, two subjects (<0.1%) reported myocarditis after vaccination with NVX-CoV2373 (on Day 11 after Dose 1, and on Day 29 after Dose 1, respectively). One subject (<0.1%) experienced myopericarditis at 73 days after the second dose of placebo in the initial vaccination period. Two subjects reported pericarditis (one on Day 29 after Dose 1 of NVX-CoV2373 [together with myocarditis], and one on Day 505 after Dose 2 of NVX-CoV2373, respectively).

Overall, among the subjects who received at least 1 dose of NVX-CoV2373, there were 61 (0.2%) deaths occurring after a dose of NVX-CoV2373, however none of these were assessed by the investigator as related to study intervention.

Among the 26,106 NVX-CoV2373 and 25,145 placebo recipients during the pre- or post-crossover periods, within 28 days after vaccination, 6 (0.2%) subjects who received a dose of NVX-CoV2373 and 2 (0.1%) subjects who received placebo reported cardiac failure and cardiomyopathy events including Cardiomyopathy, Congestive cardiomyopathy, Cardiac failure congestive, Cardiac failure, Cardiac failure acute, Left ventricular failure, Acute left ventricular failure. Additional 4 participants reported one of these AEs within 28 days of receiving a booster dose.

Reviewer's comment: Although no causality can be inferred from these observations, I defer to the clinical reviewer regarding whether further investigation is needed for these events in a post-marketing setting. Please refer to the review by the clinical reviewer for details on the safety analyses and conclusions.

Solicited AEs

Solicited local (pain at the injection site, tenderness, redness, and swelling) and systemic (fever, nausea, vomiting, headache, fatigue, malaise, muscle pain, and joint pain) reactions were collected for 7 days after each vaccination during the Initial Vaccination Period and during the Booster Vaccination Period. There were no solicited adverse reactions collected during the Crossover Period. Tables 12 and 13 show the rates of reported solicited adverse reactions by maximum severity.

Local reactions after Dose 1 were reported by 57.9% of the participants in the NVX-CoV2373 group and by 21.2% of the participants in the placebo group. After Dose 2, local reactions were reported by 74.6% and by 20.5% of participants in the NVX-CoV2373 and placebo groups, respectively. After the booster dose, local reactions were reported by 72.8% (Table 12). Pain/tenderness at the injection site was the most commonly reported reaction after NVX-CoV2373 (57.7% after Dose 1, 74.4% after Dose 2, and 72.4% after booster). Grade 3 local reactions were reported by 6.2% after Dose 2 and by 8.9% after booster of NVX-CoV2373. Additionally, there were 2 (<0.1%) subjects who reported Grade 4 local reactions (pain/tenderness) after Dose 2 of NVX-CoV2373, and 9 (<0.1%) who reported Grade 4 local reactions (pain/tenderness) after booster dose.

At least one systemic event was reported by 48.2% of the participants in the NVX-CoV2373 group and by 40.8% of the participants in the placebo group after Dose 1 (Table 12). After Dose 2, 69.0% of the participants in the NVX-CoV2373 group and 35.5% of the participants in the placebo group reported at least one systemic event. After the booster dose, 69.5% of the participants reported at least one systemic event. The most commonly reported systemic events after NVX-CoV2373 were fatigue/malaise (29.9% after Dose 1, 53.8% after Dose 2, and 55.2% after booster), muscle pain (23.3% after Dose 1, 49.9% after Dose 2, and 51.1% after booster) and headache (25.5% after Dose 1, 44.6% after Dose 2, and 44.3% after booster). Grade 3 systemic reactions were reported by 3.5% after Dose 1, by 17.1% after Dose 2 of NVX-CoV2373, and by 20.7% after booster. Additionally, Grade 4 systemic reactions were reported by 16 (<0.1%) subjects after Dose 1 of NVX-CoV2373, by 12 (<0.1%) subjects after Dose 2 of NVX-CoV2373, and by 24 (0.2%) subjects after booster dose.

Reviewer's comment: Overall, the rates of solicited adverse reactions after the second dose were higher than after the first dose, while the rates after the booster dose were, in general, similar to those after the second dose. Grades 3 and 4 solicited adverse reactions occurred more frequently after the booster dose.

Table 12. Local Injection Site Reactions Within 7 Days After Each Dose by Maximum Severity in the Initial Vaccination Period for Dose 1 and 2, and in the Booster Vaccination Period for booster dose (Safety Analysis Set)

Event	NVX-CoV2373 Dose 1 N =18334 n (%)	Placebo Dose 1 N = 9106 n (%)	NVX-CoV2373 Dose 2 N = 18323 n (%)	Placebo Dose 2 N = 8916 n (%)	NVX-CoV2373 Booster N = 11447 n (%)
Any local injection site reaction	-	-	-	-	-
Any (Grade ≥ 1)	10608 (57.9)	1926 (21.2)	13668 (74.6)	1824 (20.5)	8332 (72.8)
Grade 3	194 (1.1)	21 (0.2)	1134 (6.2)	24 (0.3)	1014 (8.9)
Grade 4	0	0	2 (< 0.1)	0	9 (< 0.1)
Pain	-	-	-	-	-
Any (Grade ≥ 1)	6277 (34.2)	1014 (11.1)	10326 (56.4)	1155 (13.0)	6453 (56.4)
Grade 3	55 (0.3)	3 (< 0.1)	301 (1.6)	7 (< 0.1)	313 (2.7)
Grade 4	0	0	1 (< 0.1)	0	6 (< 0.1)
Tenderness	-	-	-	-	-
Any (Grade ≥ 1)	9568 (52.2)	1527 (16.8)	12716 (69.4)	1329 (14.9)	7698 (67.2)
Grade 3	156 (0.9)	18 (0.2)	844 (4.6)	18 (0.2)	711 (6.2)
Grade 4	0	0	2 (< 0.1)	0	7 (< 0.1)
Pain/tenderness	-	-	-	-	-
Any (Grade ≥ 1)	10574 (57.7)	1907 (20.9)	13637 (74.4)	1806 (20.3)	8293 (72.4)
Grade 3	189 (1.0)	20 (0.2)	1005 (5.5)	22 (0.2)	859 (7.5)

Event	NVX-CoV2373 Dose 1 N =18334 n (%)	Placebo Dose 1 N = 9106 n (%)	NVX-CoV2373 Dose 2 N = 18323 n (%)	Placebo Dose 2 N = 8916 n (%)	NVX-CoV2373 Booster N = 11447 n (%)
Grade 4	0	0	2 (< 0.1)	0	9 (< 0.1)
Erythema (Redness)	-	-	-	-	-
Any (Grade ≥ 1)	165 (0.9)	28 (0.3)	1142 (6.2)	30 (0.3)	953 (8.3)
Grade 3	2 (< 0.1)	0	126 (0.7)	2 (< 0.1)	183 (1.6)
Grade 4	0	0	0	0	0
Swelling	-	-	-	-	-
Any (Grade ≥ 1)	153 (0.8)	25 (0.3)	1061 (5.8)	26 (0.3)	873 (7.6)
Grade 3	4 (< 0.1)	1 (< 0.1)	72 (0.4)	1 (< 0.1)	109 (1.0)
Grade 4	0	0	0	0	0

Source: Adapted from 2019nCoV-301 Addendum 1.0 to Adult 17-Month Clinical Study Report, dated March 12, 2024, Table 40, p. 92, submitted to STN 125817/0/4; 2019nCoV-301 Adult 17-Month Clinical Study Report, eSub 3 CSR Addendum, dated January 18, 2025, submitted to STN 125817/0/64, Table 19, p. 43.

Table 13. Systemic Reactions Within 7 Days After Dose 1, Dose 2 and Booster by Maximum Severity (Safety Analysis Set)

Event	NVX-CoV2373 Dose 1 N = 18334 n (%)	Placebo Dose 1 N = 9106 n (%)	NVX-CoV2373 Dose 2 N = 18323 n (%)	Placebo Dose 2 N = 8916 n (%)	NVX-CoV2373 Booster N = 11447 n (%)
Any systemic AE	-	-	-	-	-
Any (Grade ≥ 1)	8835 (48.2)	3713 (40.8)	12646 (69.0)	3162 (35.5)	7954 (69.5)
Grade 3	646 (3.5)	296 (3.3)	3137 (17.1)	391 (4.4)	2372 (20.7)
Grade 4	16 (< 0.1)	6 (< 0.1)	12 (< 0.1)	7 (< 0.1)	24 (0.2)
Fever	-	-	-	-	-
Any (Grade ≥ 1)	70 (0.4)	37 (0.4)	1107 (6.0)	29 (0.3)	929 (8.1)
Grade 3	9 (< 0.1)	7 (< 0.1)	81 (0.4)	6 (< 0.1)	126 (1.1)
Grade 4	7 (< 0.1)	3 (< 0.1)	2 (< 0.1)	2 (< 0.1)	6 (< 0.1)
Headache	-	-	-	-	-
Any (Grade ≥ 1)	4674 (25.5)	2141 (23.5)	8181 (44.6)	1757 (19.7)	5071 (44.3)
Grade 3	146 (0.8)	62 (0.7)	518 (2.8)	38 (0.4)	569 (5.0)
Grade 4	4 (< 0.1)	1 (< 0.1)	3 (< 0.1)	2 (< 0.1)	6 (< 0.1)
Fatigue	-	-	-	-	-
Any (Grade ≥ 1)	4774 (26.0)	2090 (23.0)	8780 (47.9)	1886 (21.2)	5708 (49.9)
Grade 3	464 (2.5)	217 (2.4)	2660 (14.5)	341 (3.8)	1969 (17.2)
Grade 4	3 (< 0.1)	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)	12 (0.1)
Malaise	-	-	-	-	-
Any (Grade ≥ 1)	2690 (14.7)	1063 (11.7)	6742 (36.8)	1038 (11.6)	4312 (37.7)

Event	NVX-CoV2373 Dose 1 N = 18334 n (%)	Placebo Dose 1 N = 9106 n (%)	NVX-CoV2373 Dose 2 N = 18323 n (%)	Placebo Dose 2 N = 8916 n (%)	NVX-CoV2373 Booster N = 11447 n (%)
Grade 3	138 (0.8)	56 (0.6)	1083 (5.9)	59 (0.7)	985 (8.6)
Grade 4	6 (< 0.1)	1 (< 0.1)	5 (< 0.1)	2 (< 0.1)	12 (0.1)
Fatigue/malaise	-	-	-	-	-
Any (Grade ≥ 1)	5488 (29.9)	2384 (26.2)	9856 (53.8)	2128 (23.9)	6323 (55.2)
Grade 3	509 (2.8)	230 (2.5)	2829 (15.4)	354 (4.0)	2102 (18.4)
Grade 4	7 (< 0.1)	1 (< 0.1)	5 (< 0.1)	3 (< 0.1)	13 (0.1)
Muscle pain (myalgia)	-	-	-	-	-
Any (Grade ≥ 1)	4273 (23.3)	1286 (14.1)	9318 (49.9)	1125 (12.6)	5852 (51.1)
Grade 3	82 (0.4)	35 (0.4)	850 (4.6)	30 (0.3)	893 (7.8)
Grade 4	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	4 (< 0.1)	11 (< 0.1)
Joint pain (arthralgia)	-	-	-	-	-
Any (Grade ≥ 1)	1413 (7.7)	600 (6.6)	3856 (21.0)	577 (6.5)	2768 (24.2)
Grade 3	53 (0.3)	29 (0.3)	419 (2.3)	24 (0.3)	522 (4.6)
Grade 4	1 (< 0.1)	0	2 (< 0.1)	2 (< 0.1)	6 (< 0.1)
Nausea/vomiting	-	-	-	-	-
Any (Grade ≥ 1)	1270 (6.9)	560 (6.1)	2085 (11.4)	482 (5.4)	1330 (11.6)
Grade 3	18 (< 0.1)	7 (< 0.1)	31 (0.2)	7 (< 0.1)	47 (0.4)
Grade 4	4 (< 0.1)	2 (< 0.1)	5 (< 0.1)	2 (< 0.1)	5 (< 0.1)

Source: Adapted from 2019nCoV-301 Adult 17-Month Clinical Study Report, eSub 3 CSR Addendum, dated January 18, 2025, submitted to STN 125817/0/64, Table 16 (p. 37), Table 22 (p. 47).

6.2 Study 2019nCoV-301 Adolescents

The Pediatric Expansion of Study 2019nCoV-301 in adolescents is an ongoing phase 3, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the effectiveness, efficacy, safety, and immunogenicity of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) in healthy and clinically stable adolescents 12 to < 18 years of age in the U.S. It was initiated on April 26, 2021. The data cutoff date for the presented results is August 6, 2022.

6.2.1 Objectives

Table 14. Study 2019nCoV-301 Pediatric Expansion in Adolescents Objectives and Endpoints

Tier	Objectives	Endpoints

Tier	Objectives	Endpoints
Primary	• To evaluate the efficacy of a 2-dose regimen of NVX-CoV2373 compared to placebo against polymerase chain reaction (PCR) confirmed symptomatic coronavirus disease 2019 (COVID-19) illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.	• First episode of PCR-positive mild, moderate, or severe COVID-19, where severity was defined as: **Mild COVID-19 (≥ 1 of the following):** • 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 onset 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. **OR Moderate COVID-19 (≥ 1 of the following):** • High fever (≥ 38.4°C) for ≥ 3 days (regardless of use of anti-pyretic medications, need not be contiguous days). • Any evidence of significant LRTI: 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).
-	-	**OR Severe COVID-19 (≥ 1 of the following):** • Tachypnea: ≥ 30 breaths per minute at rest. • Resting heart rate ≥ 125 beats per minute. • SpO_2: ≤ 93% on room air or PaO_2/FiO_2 < 300 mmHg. • High flow oxygen (O_2) therapy or NIV/NIPPV (e.g., CPAP or BiPAP). • Mechanical ventilation or ECMO.

Tier	Objectives	Endpoints
		• One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following: o Acute respiratory failure, including ARDS. o Acute renal failure. o Acute hepatic failure. o Acute right or left heart failure. o Septic or cardiogenic shock (with shock defined as SBP < 90 mm Hg OR DBP < 60 mm Hg). o Acute stroke (ischemic or hemorrhagic). o Acute thrombotic event: AMI, DVT, PE. o Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • MIS-C, as per the CDC definition: o An individual aged < 21 years presenting with fever (>38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND o No alternative plausible diagnoses; AND • Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms. • Admission to an ICU. • Death
Primary	• To describe the safety experience for the vaccine versus placebo in adolescent participants (12 to <18 years of age) based on solicited short-term reactogenicity by toxicity grade for 7 days following each vaccination (Days	**Safety Endpoints:** • Reactogenicity incidence, duration, and severity (mild, moderate, or severe) recorded by parent(s)/caregiver(s) on their electronic patient-reported outcome diary application (eDiary) on days of

Tier	Objectives	Endpoints
	0 and 21) after the initial set of vaccinations. • To assess overall safety through 49 days (28 days after second injection of each set of vaccinations [initial and crossover]) by comparing vaccine versus placebo for all unsolicited AEs and medically attended adverse events (MAAEs). • To assess the frequency and severity of MAAEs attributed to vaccine, adverse events of special interest (AESIs), or serious adverse events (SAEs) through the end of study (EoS) and to compare vaccine versus placebo after each set of vaccinations (initial and crossover). • To assess all-cause mortality in vaccine versus placebo recipients after each set of vaccinations (initial and crossover).	vaccination and subsequent 6 days (total 7 days after each vaccine injection in the initial set of vaccinations). o Reactogenicity endpoints include injection site reactions: • Pain. • Tenderness. • Erythema. • Swelling/induration. o Systemic reactions: • Fever. • Malaise. • Fatigue. • Arthralgia. • Myalgia. • Headache. • Nausea/vomiting. • Incidence and severity of MAAEs through 49 days, ie, 28 days after second injection of each set of vaccinations (initial and crossover). • Incidence and severity of unsolicited AEs through 49 days, ie, 28 days after second injection of each set of vaccinations (initial and crossover). • Incidence and severity of MAAEs attributed to trial vaccine, SAEs and AESIs through Month 12. • Incidence and severity of SAEs (including COVID-19 diagnoses), MAAEs attributed to trial vaccine and AESIs during Month 12 through Month 24 or the EoS.[1] • Death due to any cause.
Primary	• To assess non-inferiority of the neutralizing antibody response for all adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover).	**Effectiveness Endpoint:** • Neutralizing antibody response at Day 35 for all adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover).

Tier	Objectives	Endpoints

Secondary	• To evaluate the efficacy of a 2-dose regimen of NVX-CoV2373 to placebo against PCR-confirmed symptomatic COVID-19 illness due to SARS-CoV-2 variant not considered as a "variant of concern / interest" according to the CDC Variants Classification, diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.
	• To evaluate the efficacy of a 2-dose regimen of NVX-CoV2373 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second vaccination in the initial set of vaccinations of adolescent participants 12 to < 18 years of age.
	• To assess vaccine efficacy (VE) against ANY symptomatic SARS-CoV-2 infection.
	• To assess VE according to race and ethnicity.
	• To assess the durability of VE (measured by all defined efficacy endpoints) in adolescents after initial active vaccine recipients versus crossover (delayed) active vaccine recipients.[1]
	• To monitor occurrence and severity of COVID-19 cases by following participant-reported symptoms.
		• First episode of PCR-positive COVID-19, as defined under the primary endpoint, shown by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification.
		• First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
		• ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab **and** ≥ 1 of any of the following symptoms:
		  • Fever.
		  • New onset cough.
		  • New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
		  • New onset fatigue.
		  • New onset generalized muscle or body aches.
		  • New onset headache.
		  • New loss of taste or smell.
		  • Acute onset of sore throat, congestion, or runny nose.
		  • New onset nausea, vomiting, or diarrhea.
		• Proportion of adolescent participants reporting SARS-CoV-2 infection (COVID-19) from Day 28 through end of Year 1, with severity classification as defined in the **Adult Main Study** (mild, moderate, or severe).
		• Neutralizing antibody response at Day 35 for adolescent participants by age strata and with and without anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover).

Tier	Objectives	Endpoints
	• To assess the neutralizing antibody response to SARS-CoV-2 for adolescent participants by subsets with and without anti-NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover). • To assess the anti-spike IgG antibody response and hACE2 inhibiting antibody response at Day 35 for adolescent participants by subsets with and without detectable anti-NP antibodies at baseline, compared with that observed in adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover). • To assess the durability of immune response (anti-rS IgG antibody, hACE2 inhibition, and microneutralization [MN] titers) at 12, 18 and 24 months of study in all adolescent participants, and for subsets with and without detectable anti-NP antibodies at baseline or prior to crossover set of vaccinations, with that observed in adult participants 18 to < 26 years of age from the **Adult Main Study** (Immunogenicity Population participants before crossover).[1] • To assess the proportion of adolescent participants (vaccine versus placebo recipients) with SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies, including specifically undiagnosed infection, across the 2 years of study follow-up. • To assess the VE against SARS-CoV-2 infection determined by anti-SARS-CoV-2 NP antibodies in adolescent participants, regardless of whether the infection was symptomatic.	• Antibodies to SARS-CoV-2 NP at Days 0 and 35, and at specified time points until Month 24 were to be used to determine natural infection and to determine the incidence of undiagnosed infection acquired during study follow-up. • Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers 14 days after second injection of the initial vaccination series (Day 35) in adolescent participants and subsets with and without anti-NP antibodies at baseline. • Serum IgG levels to SARS-CoV-2 S protein, MN and hACE2 inhibition titers at specified time points until Month 24.[1] • Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form. • Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.[1]

Tier	Objectives	Endpoints
Post-Booster	• To assess the incidence of PCR-confirmed symptomatic COVID-19 (as defined above) following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants. • To assess the incidence of PCR-confirmed symptomatic COVID-19 due to a SARS-CoV-2 variant not considered as a "variant of concern/interest" according to the CDC Variants Classification following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants. • To assess the incidence of PCR-confirmed symptomatic COVID-19 due to a SARS-CoV-2 variant considered as a "variant of concern/interest" according to the CDC Variants Classification following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants. • To assess the incidence of PCR-confirmed moderate-to-severe symptomatic COVID-19 (as defined above) following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants.	• First episode of PCR- positive mild, moderate, or severe COVID-19 (as defined above) occurring ≥ 7 days after the booster vaccine dose. First episode of PCR-positive COVID- 19 (as defined above) occurring ≥ 7 days after the booster vaccine dose and shown by gene sequencing to represent a variant not considered as a "variant of interest/concern" according to the CDC Variants Classification. • First episode of PCR-positive COVID-19 (as defined above) occurring ≥ 7 days after the third(booster) vaccine dose and shown by gene sequencing to represent a "variant of concern/interest" according to the CDC Variants Classification. • First episode of PCR-positive moderate-to-severe COVID-19 (as defined above) occurring ≥ 7 days after the booster vaccine dose. • Neutralizing antibody titers, serum levels of IgG to SARS-CoV-2 S protein and hACE2 inhibition titers from Immunogenicity Population immediately prior and at 28 days after administration of the booster vaccine dose. • Positive anti-NP antibody titers at any pre-specified time point following the booster vaccine dose in participants with no intervening symptoms of COVID-19. • Immune response after the booster vaccine dose by neutralizing antibody titer and IgG antibody to SARS CoV-2 rS protein and by hACE2 inhibition titers at prespecified time points through EoS in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies. • PCR-confirmed SARS-CoV-2 infection detected in participants without symptoms of COVID-19 illness based on NP swabs obtained at prespecified time points after booster injections. • Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case occurring ≥ 7 days after the booster vaccine dose via the Endpoint Form.

Tier	Objectives	Endpoints
	• To assess the incidence of any PCR-confirmed symptomatic or moderate-to-severe symptomatic COVID-19 (as defined above) following a booster vaccine dose administered no less than 5 months after completion of active vaccination (initial or crossover series) for adolescent participants and no less than 6 months after completion of active vaccination (initial or crossover series) for adult participants. • To assess the incidence of development of anti-NP antibodies following a booster vaccine dose among participants without intervening symptomatic COVID-19.[1] • To describe the humoral immune response at 28 days after the booster vaccine dose in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population Participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable pre-booster vaccine dose anti-NP antibodies. • To assess the immune response at 28 days after the booster vaccine dose by IgG antibody to SARS-CoV-2 S protein and hACE2 inhibition titers in all Immunogenicity Population Participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies. • To assess the durability of immune response after the booster vaccine dose by neutralizing antibody titer and IgG antibody to SARS CoV-2 rS protein and by hACE2 inhibition titers at prespecified time points through EoS in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies.[1] • To assess the level of humoral immune response following the booster vaccine dose in comparison to that after completion of the initial active Novavax vaccination series. • To assess overall safety through 28 days after the booster vaccine dose. • To assess the frequency and severity of MAAEs attributed to vaccine,	• Reactogenicity (as defined above) incidence and severity (mild, moderate, or severe) recorded by all participants on their electronic patient-reported outcome diary application (eDiary) on days of the booster vaccination and subsequent 6 days. • Incidence and severity of unsolicited AEs through 28 days after the booster vaccine dose. • Incidence and severity of MAAEs attributed to trial vaccine, SAEs and AESIs through EoS. • Death due to any cause.

Tier	Objectives	Endpoints
	AESIs, or SAEs through EoS. • To assess all-cause mortality after a booster vaccine dose.	

[1] Objectives/endpoints not addressed in the submitted interim report due to incompleteness or as yet unavailable data.
Source: Adapted from 2019nCoV-301: 12-Month Adolescent Clinical Study Report, dated January 18, 2025, submitted to STN 125817/0/4, Table 3, p. 30.

6.2.2 Design Overview

The study design for the Pediatric Expansion was similar to the Adults Study (Table 15). Approximately 3000 adolescents 12 to <18 years old from the U.S. were planned to be enrolled and randomized in a 2:1 ratio to receive a primary series of two doses of NVX-CoV2373 or placebo, 21 days apart. Subjects' vaccination was planned to be contingent on favorable early safety data (i.e., 7 days of reactogenicity and overall safety post dose 1) from a sentinel cohort of 60 adolescents (30 of age 15 to <18 years old, and 30 of age 12 to <15 years old), assessed for each dose. Blinded crossover to the alternate product was planned approximately 6 months after completion of the primary series.

The protocol included also a "Booster Amendment", according to which a booster dose was planned to be administered at least 5 months after completion of the primary series. For the immunogenicity analysis for the booster, a subset of subjects receiving a booster dose was included.

Table 15. Study Design for 2019nCoV-301 Adolescents

Arm	Planned Sample Size	Initial Vaccination Period	Crossover Vaccination Period	Booster Vaccination Period
-	-	2 doses (21 days apart)	2 doses (21 days apart)	1 dose (≥ 5 m. after an active Primary Series)
NVX-CoV2373	N up to 2,000: 12 - <18 years of age	NVX-CoV2373	Placebo	NVX-CoV2373
Placebo	N up to 1,000: 12 - <18 years of age	Placebo	NVX-CoV2373	NVX-CoV2373

Note: NVXCoV2373 refers to Intramuscular (IM) injection of the Original Wuhan formulation SARS-CoV-2 rS [5 µg] + Matrix-M1 adjuvant [50 µg]; Placebo refers to IM injection of normal saline.
Source: Adapted from 2019nCoV-301 Pediatric Expansion Study SAP, Version 6.1, dated April 26, 2023, submitted to STN 125817/0/4, Table 1, p. 14.

Solicited Adverse Reactions (local and systemic reactogenicity) were planned to be reported by participants' parent(s)/caregiver(s) via eDiary for 7 days after each dose during the Initial Vaccination Period. Unsolicited AEs and MAAEs were to be collected for 49 days (i.e., 28 days after second injection of the initial and crossover series). Follow-up for MAAEs, AESIs, SAEs was to be conducted through study completion.

The study included surveillance for COVID-19 for the assessment of the efficacy endpoints starting on Day 4 through the end of study EoS. Parent(s)/caregiver(s) were

asked to collect symptoms of COVID-19 and to report them to the study sites. Upon report of symptoms of COVID-19, an in-person Acute Illness Visit was planned to be performed for examination of the participants, collection of a medically attended nasal swab and a blood sample for serologic testing. The medically attended swabs were to be shipped to the central laboratory at the University of Washington. Participants who were confirmed to be PCR-positive for SARS-CoV-2 (by the central lab) would be scheduled for a Convalescent Visit (approximately 1 month after the onset of the PCR-confirmed case) to record the clinical course of the disease on the Endpoint Assessment Form and to obtain a blood sample for convalescent serologic testing. Participants who report a positive test for COVID-19 outside of the study would be asked to complete a Convalescent Visit, however, these cases were not planned to be included in the primary endpoint cases.

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) were planned to be collected from all participants before the first vaccination and at select subsequent time points, including prior to the crossover set of vaccinations. Immunogenicity testing and nasal swab for PCR testing were also planned to be collected immediately prior to the booster dose and at 28 days after.

6.2.3 Population

The Pediatric Expansion study included adolescents from the U.S. of age 12 to <18 years old, who were determined by the investigator as being healthy or medically stable.

6.2.4 Study Treatments or Agents Mandated by the Protocol

- **NVXCoV2373** - Original Wuhan formulation of SARS-CoV-2 rS (5 μg) + Matrix-M1 adjuvant (50 μg), administered as an Intramuscular (IM) injection.
- **Placebo** – normal saline, administered as an IM injection.

6.2.6 Sites and Centers

The study was conducted at 73 sites across the U.S.

6.2.8 Hypotheses and Criteria for Study Success

The Pediatric Expansion study included a primary efficacy objective; however, it was specified as descriptive in nature, and no hypothesis testing was planned to evaluate it. Furthermore, the effectiveness of NVX-CoV-2373 in adolescents was assessed based on an immunobridging strategy that included hypothesis testing for noninferiority of the immune response following vaccination with two doses (primary series) of NVX-CoV-2373 in adolescents compared to the immune response following vaccination with two doses of NVX-CoV-2373 in adults 18 -< 26 years from the Adults portion of study 2019nCoV-301.

Noninferiority Immunogenicity Objective for the Primary Series (Immunobridging):

For this objective, it was pre-specified that non-inferiority of immune response based on neutralization titers for adolescents 12 -< 18 years of age compared to adults 18 -< 26 years of age (from the Adults portion of study 2019nCoV-301), will be demonstrated by testing the following hypotheses:

$$H_{01}: GMT_{12-<18yo} / GMT_{18-<26yo} \leq 0.67 \text{ vs } H_{a1}: GMT_{12-<18yo} / GMT_{18-<26yo} > 0.67,$$

$$H_{02}: SCR_{12-<18yo} - SCR_{18-<26yo} \leq -10\% \text{ vs } H_{a2}: SCR_{12-<18yo} - SCR_{18-<26yo} > -10\%,$$

where $GMT_{12-<18yo}$ refers to the GMTs against SARS-CoV-2 Wild-Type virus (Ancestral Wuhan Strain) at 14 days after the second dose of the primary series of NVX-CoV2373 in adolescents in the Pediatric Expansion study, and $GMT_{18-<26yo}$ refers to the respective GMTs at Day 35, i.e., 14 days after dose 2 in the initial set of vaccinations in the Adults portion of the study. $SCR_{12-<18yo}$ and $SCR_{18-<26yo}$ refer to the respective SCRs. Seroconversion was defined on the subject level as having ≥ 4-fold increase from baseline if the baseline value is above or equal to the assay's LLOQ or having a post-baseline value ≥ 4 times the LLOQ if the baseline is below the assay's LLOQ. SCR is the percentage of subjects achieving seroconversion. The success criteria for demonstrating noninferiority of immunogenicity for primary series in adolescents 12 -< 18 years of age compared to adults 18 -< 26 years of age were i) the LB of the 95% CI of the GMR = $GMT_{12-<18yo} / GMT_{18-<26yo}$ is > 0.67, ii) the point estimate of the GMR is > 0.82, and iii) the LB of the 95% CI of $SCR_{12-<18yo} - SCR_{18-<26yo}$ is >-10%.

Noninferiority Booster Immunogenicity Objective:

$$H_{01}: GMT_{booster} / GMT_{D35} \leq 0.67 \text{ vs } H_{a1}: GMT_{booster} / GMT_{D35} > 0.67,$$

$$H_{02}: SCR_{booster} - SCR_{D35} \leq -10\% \text{ vs } H_{a2}: SCR_{booster} - SCR_{D35} > -10\%,$$

where $GMT_{booster}$ refers to the GMTs against SARS-CoV-2 Wild-Type virus (Ancestral Wuhan Strain) at 28 days after a single booster dose, and GMT_{D35} refers to the respective GMTs at Day 35, i.e., 14 days after dose 2 in the initial set of vaccinations. For the $SCR_{booster}$ estimation, baseline is the value measured on the day of the first dose prior to vaccination. The success criteria for demonstrating noninferiority of booster immunogenicity objective were i) the LB of the 95% CI of the GMR = $GMT_{booster} / GMT_{D35}$ is > 0.67, ii) the point estimate of the GMR is > 0.83, and iii) the LB of the 95% CI of $SCR_{booster} - SCR_{D35}$ is >-10%.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for study 2019nCoV-301 Pediatric Expansion (version 6.1, dated April 26, 2023) was submitted with the application in STN 125817/0. A brief overview of the SAP is presented below.

Analysis populations: The definitions of the study Analysis Populations were the same as those for the Adults portion of the study and are shown in Table 4. The primary population for the primary immunogenicity objective was the PP-IMM Analysis Set. The

primary population for the descriptive efficacy analyses was the PP-EFF Population. The primary population for safety analyses was the Safety Analysis Set.

Noninferiority Immunogenicity Analysis for the Primary Series (Immunobridging)
For the primary noninferiority immunogenicity analysis for the primary series, a random sample of ~750 participants from the Pediatric Expansion study and ~750 participants aged 18-<26 years of age from the Adult Main Study were planned to be drawn to provide approximately 400 participants for the NI analysis (taking in to account the 2:1 randomization ratio and 20% non-evaluability).

Formal hypothesis testing was planned to be conducted for this objective. The GMTR between the two age cohorts and the corresponding two-sided 95% CI were to be estimated based on the log-transformed titers using an analysis of covariance (ANCOVA) with age cohort and baseline (Day 0) measurement as the covariate, and then back-transformed to the original scale. The difference in SCRs between the two age cohorts was to be computed together with a two-sided 95% CI using the method of Miettinen and Nurminen.

Analysis for the Primary Efficacy Endpoint for the Primary Series
The statistical method used for this endpoint was planned to be the same as the one used in the Adult Main Study (see Section 6.1.9), however, here it is planned as descriptive in nature with no hypothesis testing.

Noninferiority Immunogenicity Analysis for the Booster Dose
This analysis included subjects who have received NVX-CoV2373 as a primary series in the Initial Vaccination Period, who had all four timepoints (baseline, Day 35, pre-booster, 28 days after booster dose) evaluated and who met the definition of the Booster PP-IMM Analysis Set. The 95% CI for the GMTs and for the GMTR were calculated based on the paired t-test using the log-transformed values, and then back transformed to the original scale. The 95% CI for the SCRs were based on the Clopper-Pearson method. The difference in the SCRs was based on the Tango method.

Analyses for the Safety Endpoints
Safety endpoints were summarized by vaccine group according to the study intervention that the participants actually received (Safety Analysis Set). The proportion of participants reporting each safety endpoint and the respective 95% CI based on the Clopper-Pearson method were reported.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The data cut-off date for the study results that were submitted to the BLA is August 6, 2022. The Pediatric Expansion of Study 2019nCoV-301 was initiated on April 26, 2021. There were 2247 subjects who were randomized to receive NVXCoV2373 (N=1491) or placebo (N=756) (Table 16). Of the randomized participants, 2232 (99.3%) were vaccinated with at least 1 dose, and 2198 (97.8%) were vaccinated with 2 doses. A

slightly larger percentage of subjects in the placebo arm (7.8%) discontinued during the Initial vaccination period compared to the NVXCoV2373 arm (5.6%). The majority of the discontinuations were after the second dose (n=66 [4.4%] in the NVXCoV2373 arm, and n=45 [6.0%] in the placebo arm). The main reason for discontinuation was due to withdrawal by the participant. During the blinded crossover vaccination period, a total of 1353 (90.7%) subjects from the NVX-CoV2373 arm and a total of 667 (88.2%) subjects from the placebo arm received at least one dose of the alternate product. Booster vaccination was initiated on April 4, 2022. A total of 1499 (66.7%) participants received a booster dose of NVX-CoV2373.

Overall, as of the data cutoff date, none of the subjects had completed the study, and 236 (15.8%) in the NVXCoV2373 arm and 158 (20.9%) in the placebo arm have discontinued the study.

Table 16. Disposition of Participants (as Randomized)

Population	**NVXCoV2373 N[1]=1491 n (%)**	**Placebo N[1]=756 n (%)**	**Total N[1]=2247 n (%)**
Initial Vaccination Period:	-	-	-
Completed at least 1 dose	1484 (99.5)	748 (98.9)	2232 (99.3)
Completed 2 doses	1465 (98.3)	733 (97.0)	2198 (97.8)
Discontinued from initial vaccination period	83 (5.6)	59 (7.8)	142 (6.3)
Reason for discontinuation:	-	-	-
Withdrawal by participant	60 (4.0)	45 (6.0)	105 (4.7)
Lost to follow-up	18 (1.2)	12 (1.6)	30 (1.3)
Other	5 (0.3)	2 (0.3)	7 (0.3)
Adverse event	0	0	0
Death	0	0	0
Crossover Period:	-	-	-
Completed dose 3	1353 (90.7)	667 (88.2)	2020 (89.9)
Completed dose 4	1338 (89.7)	658 (87.0)	1996 (88.8)
Discontinued during the crossover vaccination period	123 (8.2)	73 (9.7)	196 (8.7)
Reason for discontinuation:	-	-	-
Withdrawal by participant	78 (5.2)	41 (5.4)	119 (5.3)
Lost to follow-up	37 (2.5)	23 (3.0)	60 (2.7)
Other	8 (0.5)	9 (1.2)	17 (0.8)
Death	0	0	0
Adverse event	0	0	0
Booster Period:	-	-	-
Received a booster dose[2]	1009 (67.7)	490 (64.8)	1499 (66.7)
Discontinued on/after booster	50 (3.4)	35 (4.6)	85 (3.8)
Reason for discontinuation:	-	-	-
Lost to follow-up	16 (1.1)	12 (1.6)	28 (1.2)
Withdrawal by participant	27 (1.8)	17 (2.2)	44 (2.0)

Population	NVXCoV2373 N[1]=1491 n (%)	Placebo N[1]=756 n (%)	Total N[1]=2247 n (%)
Other	6 (0.4)	6 (0.8)	12 (0.5)
Death	0	0	0
Adverse event	1 (< 0.1)	0	1 (< 0.1)
Overall:	-	-	-
Completed	0	0	0
Ongoing[3]	1255 (84.2)	598 (79.1)	1853 (82.5)
Discontinued	236 (15.8)	158 (20.9)	394 (17.5)
Reason for discontinuation:	-	-	-
Withdrawal by participant	155 (10.4)	102 (13.5)	257 (11.4)
Lost to follow-up	61 (4.1)	40 (5.3)	101 (4.5)
Other	20 (1.3)	16 (2.1)	36 (1.6)
Death	0	0	0
Adverse event	0	0	0
Trial vaccine blind broken by site	134 (9.0)	73 (9.7)	207 (9.2)
Reason for unblinding:	-	-	-
Unblinded with the intention to receive EUA vaccine	95 (6.4)	52 (6.9)	147 (6.5)
Other reasons	39 (2.6)	21 (2.8)	60 (2.7)

[1] Denominator in the respective group.
[2] Both arms received NVXCoV2373 as a booster dose.
[3] As of the data cutoff date (August 6, 2022).
Source: Created by the reviewer based on the submitted data and the information provided in 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, Tables 14-15 (p. 92-93); 2019nCoV-301 6-Month Booster Safety Addendum to 12-Month Adolescent Clinical Study Report, dated July 19, 2023, Table 4 (p. 19) submitted to STN 125817/0/4.

For the initial vaccination period (i.e., the earliest of early termination, death, first crossover dose, booster dose, or data cutoff), the median follow-up time after the first dose was 3.1 months (range 0.3-15.0), and the median follow-up after the second dose was 2.3 months (range 0.1-14.4) with 85 (3.8%) subjects have completed at least 6 months of follow-up during that period. Of the vaccinated subjects, 2206 (98.8%) subjects had completed at least 1 month of follow-up after dose 2.

Table 17 shows the analysis populations (see Table 4 for the definitions). Of the 1484 subjects who were randomized to NVX-CoV2373 and were vaccinated (FAS), 1 received two doses of placebo instead, and of the 748 subjects who were randomized to placebo and were vaccinated (FAS), 4 received at least one dose of NVX-CoV2373. Thus, the Safety Population included a total of 1487 participants who have received at least one dose of NVX-CoV2373 and 745 participants who have received placebo during the Initial Vaccination Period. The PP-IMM Day 35 analysis population included 1126 subjects in the NVX-CoV2373 arm and 537 subjects in the placebo arm. The most frequent reason for exclusion from the PP-IMM Day 35 analysis population was due to a baseline positive anti-NP result (15.6%). A total of 1499 participants received a booster dose of NVX-CoV2373 and were included in the Booster Safety Analysis Set. Of the 220

participants who were sampled from the Booster Safety Analysis Set for inclusion in the Booster PP-IMM Analysis Set, 122 participants were included.

Table 17. Analysis Populations

Analysis Sets	**NVX-CoV2373 N = 1491 n (%)**	**Placebo N = 756 n (%)**	**Total N = 2247 n (%)**
ITT	1491 (100)	756 (100)	2247 (100)
Not dosed	7 (0.5)	8 (1.1)	15 (0.7)
FAS[1]	1484 (99.5)	748 (98.9)	2232 (99.3)
Safety Analysis Set	1487	745	2232
PP-EFF[2]	1199 (80.8)	589 (78.7)	1788 (80.1)
Excluded:	285 (19.2)	159 (21.3)	444 (19.9)
Baseline positive anti-NP result	227 (15.3)	121 (16.2)	348 (15.6)
Baseline positive PCR result	12 (0.8)	9 (1.2)	21 (0.9)
Did not complete vaccination schedule	19 (1.3)	15 (2.0)	34 (1.5)
Censored prior to observation period	38 (2.6)	25 (3.3)	63 (2.8)
Protocol Deviation	15 (1.0)	16 (2.1)	31 (1.4)
Death	0	0	0
Unblinded	19 (1.3)	8 (1.1)	27 (1.2)
Post-baseline Positive PCR episode	5 (0.3)	4 (0.5)	9 (0.4)
Withdrawal from Study	1 (<0.1)	1 (0.1)	2 (<0.1)
PP-EFF-2[2]	1427 (96.2)	708 (94.7)	2135 (95.7)
PP-IMM Day 35[2]	1126 (75.9)	537 (71.8)	1663 (74.5)
Excluded:	358 (24.1)	211 (28.2)	569 (25.5)
Sample not collected (Baseline or Subsequent Visit)	78 (5.3)	55 (7.4)	133 (6.0)
Baseline Positive Anti-NP result	227 (15.3)	121 (16.2)	348 (15.6)
Did not complete vaccination schedule	19 (1.3)	15 (2.0)	34 (1.5)
Baseline positive PCR results	12 (0.8)	9 (1.2)	21 (0.9)
Protocol Deviation	67 (4.5)	42 (5.6)	109 (4.9)
Positive PCR result Prior to Visit	7 (0.5)	6 (0.8)	13 (0.6)
PP-IMM-2 Day 35[2]	1333 (89.8)	647 (86.5)	1980 (88.7)
Booster Safety Set[3]	1009	490	1499
Booster PP-IMM[3,4]	57 (5.6)	65 (13.3)	122 (8.1)

[1] Percentages were calculated based on randomized (ITT set) participants in each column.
[2] Percentages were calculated based on the FAS in each column.
[3] All subjects in this set received NVX-CoV2373 as a booster dose during the booster period.
[4] Percentages were calculated based on the Booster Safety Analysis Set.
Source: Adapted from 2019nCoV-301 Addendum 1.0 to 12-Month Adolescent Clinical Study Report, dated March 6, 2024, submitted to STN 125817/0/4, Tables 3-5, p. 19.

6.2.10.1.1 Demographics

Table 18 shows the demographic and baseline characteristics by study group for the Safety Population. The characteristics were comparable between the study groups. For the PP-IMM Day 35 Analysis Set, the demographic and baseline characteristics were distributed similarly and were also comparable between the two study arms.

Table 18. Demographic and Baseline Characteristics (Safety Population)

Characteristic	NVX-CoV2373 N = 1487	Placebo N = 745	Total N = 2232
Age (years)	-	-	-
Mean (SD)	13.9 (1.41)	13.8 (1.44)	13.8 (1.42)
Median (range)	14.0 (12, 17)	14.0 (12, 17)	14.0 (12, 17)
Age group, n (%)	-	-	-
12 to < 15 years	997 (67.0)	500 (67.1)	1497 (67.1)
15 to < 18 years	490 (33.0)	245 (32.9)	735 (32.9)
Sex, n(%)	-	-	-
Male	756 (50.8)	416 (55.8)	1172 (52.5)
Female	731 (49.2)	329 (44.2)	1060 (47.5)
Race, n (%)	-	-	-
White	1115 (75.0)	545 (73.2)	1660 (74.4)
Black or African American	202 (13.6)	108 (14.5)	310 (13.9)
American Indian or Alaska Native	32 (2.2)	14 (1.9)	46 (2.1)
Asian	43 (2.9)	34 (4.6)	77 (3.4)
Mixed origin	82 (5.5)	37 (5.0)	119 (5.3)
Native Hawaiian or Other Pacific Islander	3 (0.2)	2 (0.3)	5 (0.2)
Not Reported	10 (0.7)	5 (0.7)	15 (0.7)
Ethnicity, n (%)	-	-	-
Not Hispanic or Latino	1208 (81.2)	607 (81.5)	1815 (81.3)
Hispanic or Latino	274 (18.4)	138 (18.5)	412 (18.5)
Not Reported	2 (0.1)	0	2 (<0.1)
Unknown	3 (0.2)	0	3 (0.1)
BMI (kg/m^2)	-	-	-
Mean (SD)	24.25 (6.922)	23.71 (6.764)	24.07 (6.873)
Median (range)	22.60 (14.0, 59.4)	21.90 (10.0, 63.8)	22.30 (10.0, 63.8)
BMI (kg/m) category, n (%)[1]	-	-	-
Underweight	40 (2.7)	28 (3.8)	68 (3.0)
Healthy Weight	771 (51.8)	417 (56.0)	1188 (53.2)
Overweight	270 (18.2)	107 (14.4)	377 (16.9)
Obese	406 (27.3)	193 (25.9)	599 (26.8)
Occupation, n (%)	-	-	-
Student attending school in person	-	-	-

Characteristic	NVX-CoV2373 N = 1487	Placebo N = 745	Total N = 2232
Yes	1049 (70.5)	534 (71.7)	1583 (70.9)
No	438 (29.5)	211 (28.3)	649 (29.1)
SARS-CoV-2 Serostatus, n (%)	-	-	-
Anti-NP/PCR[2] Positive	234 (15.7)	125 (16.8)	359 (16.1)
Anti-NP/PCR[2] Negative	1253 (84.3)	620 (83.2)	1873 (83.9)
Missing	0	0	0

[1] BMI was classified as follows (using gender and age specific percentiles): Underweight = participants less than the 5th percentile; Healthy weight =participants within the 5th percentile and up to the 85th percentile; Overweight = participants within the 85th percentile to less than the 95th percentile; Obesity = participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.
[2] Participants with either anti-NP or PCR are reported.
Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 30, p. 107.

6.2.11 Immunogenicity and Efficacy Analyses

The effectiveness of NVX-CoV-2373 in adolescents was assessed based on an immunobridging strategy that included hypothesis testing for noninferiority of the immune response following vaccination with two doses (primary series) of NVX-CoV-2373 in adolescents compared to the immune response following vaccination with two doses of NVX-CoV-2373 in adult participants, 18 -< 26 years of age, from the Adults portion of study 2019nCoV-301.

6.2.11.1 Analyses of Primary Endpoints

The SAP specified that there would be no interim analyses in the study. The applicant conducted evaluation of the primary efficacy endpoint based on a data cutoff date of October 6, 2021 (included in the EUA). However, in the study CSR (dated July 21, 2023), it is stated that there were late arriving data. In this BLA, the applicant submitted results based on a data cutoff date of August 6, 2022. This review memo discusses the results based on this data cutoff date.

Primary Immunogenicity Endpoint (Immunobridging)

The results from the primary immunogenicity analyses comparing the immune response after vaccination with NVX-CoV-2373 in adolescents (seronegative to anti-SARS-CoV-2 NP antibodies/PCR-negative at baseline) at Day 35 (14 days after Dose 2) to that in young adults (18 to < 26 years of age, seronegative to anti-SARS-CoV-2 NP antibodies/PCR-negative at baseline) from the Adults portion of study 2019nCoV-301 are shown in Table 19.

The Day 35 MN assay neutralizing antibody GMTs against the original Wuhan serotype (SARS-CoV-2 S Wild-Type Virus) in adolescent participants was 3791.2, 95% CI (3411.6, 4213.1), and in young adults, the respective GMTs was 2603.3, 95% CI (2359.1, 2872.9). The respective GMTR was 1.5, 95% CI (1.3, 1.7). The SCR for the adolescent participants was 98.9%, 95% CI (97.5%, 99.7%), and for the young adults, it was 99.3%,

95% CI (97.9%, 99.8%). The respective SCR difference was -0.3%, 95% CI (-1.9%, 1.2%).

Reviewer's comment: The study success criteria (Section 6.2.8) for the primary immunogenicity objective for immunobridging were met, as the LB of the 95% CI for the GMTR was >0.67, the point estimate of GMTR was >0.82, and the LB of the 95% CI for the SCR difference was >-10%.

Table 19. Immunogenicity Analyses - MN Assay Neutralizing Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 Overall and Stratified by Age Group (PP-IMM Analysis Set)

Parameters	**Adolescents (12 to < 18 Years)**	**Adults (18 to < 26 Years)**	**Parameter**
Day 0	-	-	-
n	466	413	-
GMT	10.3	10.2	-
95% CI[1]	(10.0, 10.6)	(10.0, 10.4)	-
Day 35	-	-	-
n	466	413	**GMTR, 95% CI[2]**
GMT	3791.2	2603.3	1.5 (1.3, 1.7)
95% CI[1]	(3411.6, 4213.1)	(2359.1, 2872.9)	-
Day 35 seroconversion	-	-	-
n3	461	410	**Difference, 95% CI[4]**
SCR %[3]	98.9	99.3	-0.3 (-1.9, 1.2)
95% CI[3] (%)	(97.5, 99.7)	(97.9, 99.8)	-

[1] The 95% CI for GMT was calculated based on the t-distribution.
[2] An ANCOVA with age cohort as main effect and baseline MN Assay neutralizing antibodies as covariate was performed to estimate the GMTR. Individual response values that were below the LLOQ were set to half LLOQ.
[3] SCR was defined as the percentage of subjects at Day 35 visit with a ≥ 4 fold rise from Day 0 if Day 0 value was equal to or above LLOQ, or at least 4-fold rise from LLOQ if Day 0 value was below LLOQ in antibody concentration. The 95% CI for SCR was based on the Clopper-Pearson exact method.
[4]. The 95% CI for the difference in SCRs was based on the method of Miettinen and Nurminen.
Note: The table includes results for the active vaccine group only.
Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 54, p. 141.

In a descriptive subgroup analysis by age subgroup, the GMTR for adolescents 12 to <15 years of age (n=310) versus young adults 18 to <26 years of age was 1.6, 95% CI (1.4, 1.8), and the SCR difference was 0.1%, 95% CI (-1.7%, 1.6%). For the subgroup of adolescents 15 to <18 years of age (n=156), the respective GMTR was 1.2, 95% CI (1.0, 1.5), and the SCR difference was -1.2%, 95% CI (-4.8%, 0.6%).

Reviewer's comment: The descriptive subgroup analyses by age subgroup were consistent with the primary immunogenicity analysis.

Analysis for the Primary Efficacy Endpoint for the Primary Series
For adolescents, the efficacy analyses were of descriptive nature and there was no hypothesis testing planned for this objective.

In the PP-EFF Analysis Set, at the time of the data cut-off date, there were a total of 20 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after the second vaccination in the Initial Vaccination Period accrued (Table 20). Of these cases, 6 were in the NVX-CoV2373 group and 14 were in the placebo group. There was 1 moderate case in the placebo group. The rest of the cases were mild. The VE of NVX-CoV2373 against symptomatic mild, moderate, or severe COVID-19 in baseline seronegative adolescent participants was 79.82% (95% CI: 47.55%, 92.24%).

Table 20. Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 with Onset from at Least 7 Days after Second Vaccination of the Pre-Crossover Vaccination Period in Adolescent Participants (PP-EFF Analysis Set)

Parameter	NVX-CoV2373 N = 1199	Placebo N = 589	VE [2] % 95% CI
Participants with occurrence of event [1], n (%)	6 (0.5)	14 (2.4)	79.82 (47.55, 92.24)
Severity of first occurrence, n (%)	-	-	-
Mild	6 (0.5)	13 (2.2)	-
Moderate	0	1 (0.2)	-
Severe	0	0	-
Median (range) surveillance time [3] (days)	64.0 (1, 379)	63.0 (1, 153)	-
Mean Disease Incidence Rate (per 100-person-years), 95% CI	2.89 (1.30, 6.43)	14.32 (8.49, 24.13)	-

[1] As per the definition in Table 2.
[2] Modified Poisson regression with logarithmic link function, vaccine group as fixed effects and robust error variance [Zou 2004].
[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. Participants were censored at the earliest of (i) cut-off date (06 August 2022), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) end of follow-up, (vi) first dose of crossover, or (vii) booster dose.
Source: Adapted from 2019nCoV-301 Addendum 1.0 to 12-Month Adolescent Clinical Study Report, dated March 6, 2024, Table 8, p. 28, submitted to STN 125817/0/4.

The applicant conducted supportive analysis in the PP-EFF-2 Analysis Set (i.e., regardless of baseline serostatus). There were 21 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 - 6 (all mild cases) in the NVX-CoV2373 group and 15 (14 mild, and 1 moderate) in the placebo group. The respective VE was 80.88% (95% CI: 50.77%, 92.58%), which was similar to the primary VE analysis. The applicant additionally conducted subgroup analyses by demographic characteristics, however, these were of limited value due to the small numbers of cases that were accrued in the subgroups.

6.2.11.2 Analyses of Secondary Endpoints

Noninferiority Immunogenicity Analysis for the Booster Dose

This analysis included subjects who had received NVX-CoV2373 as a primary series in the Initial Vaccination Period, who had all four timepoints (baseline, Day 35, pre-booster,

28 days after booster dose) evaluated and who met the definition of the Booster PP-IMM Analysis Set. The 95% CI for the GMTs and for the GMTR were calculated based on the t-distribution using the log-transformed values, and then back transformed to the original scale. The 95% CI for the SCRs were based on the Clopper-Pearson method. The difference in the SCRs was based on the Tango method.

Table 21 shows the noninferiority immunogenicity results for the booster dose (administered at least 5 months after completion of the primary series) in adolescents. The GMT against the original Wuhan serotype at 28 days post booster dose was 12177.5, 95% CI (9294.6, 15954.6), and at Day 35 (14 days after the second dose of NVX-CoV2373) the respective GMT was 4305.4, 95% CI (3543.7, 5230.7). The respective GMTR was 2.8, 95% CI (2.1, 3.8). The SCR at 28 days post booster dose was 100%, 95% CI (93.6%, 100.0%), and Day 35 (14 days after the second dose of NVX-CoV2373), it was 100%, 95% CI (93.6%, 100.0%). The respective SCR difference was 0, 95% CI (-6.4%, 6.4%).

Reviewer's comment: The success criteria for the immunogenicity booster objective (Section 6.2.8) were met, as the LB of the 95% CI for the GMTR was >0.67, the point estimate of GMTR was >0.83, and the LB of the 95% CI for the SCR difference was > -10%.

Table 21. GMTR and SCR of Neutralizing Antibody Titers (MN50) Against SARS-CoV-2 Wild-Type Virus (Ancestral Wuhan Strain) in Booster PP-IMM Analysis Set

Parameters	**Time of first dose of NVX-CoV2373 N=56**	**14 days after second dose of NVX-CoV2373 N=56**	**Time of booster dose of NVX-CoV2373 N=56**	**28 days post-booster dose of NVX-CoV2373 N=56**
Titers Median (range)	10.0 (10, 160)	5120.0 (640, 20480)	320.0 (40, 20480)	10240.0 (2560, 81920)
GMT, 95% CI[1]	10.6 (9.6, 11.8)	4305.4 (3543.7, 5230.7)	420.2 (284.8, 619.9)	12177.5 (9294.6, 15954.6)
SCR %, 95% CI[2,4]	-	100.0 (93.6, 100.0)	-	100.0 (93.6, 100.0)
GMTR, 95% CI[1,5]	-	-	-	2.8 (2.1, 3.8)
SCR % Difference, 95% CI[3,5]	-	-	-	0 (-6.4, 6.4)

[1] The 95% CI for GMT and GMTR were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
[2] Based on Clopper-Pearson.
[3] Based on Tango method.
[4] SCR at 28 days post-booster is relative to time of first dose of NVX-CoV2373.
[5] Comparison between 28 days post-booster dose and 14 days after second dose of NVX-CoV2373.
Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 60, p. 153.

6.2.12 Safety Analyses

This section summarizes the main safety analysis results for adolescents. The safety analyses were descriptive in nature, and no formal hypothesis testing was planned. For a more detailed discussion of the safety results, please refer to the clinical review memo by Dr. Charles Line.

Unsolicited AEs

A summary of the rates of unsolicited AEs for study participants vaccinated during the Initial Vaccination Period, the Crossover Vaccination Period and the Booster Period are shown in Table 22. During the Initial Vaccination Period, the rates of unsolicited AEs were similar between the two groups (16.1% versus 16.6%). The most frequently reported unsolicited AEs within 49 days of the first vaccination were of the SOC of Infections and Infestations - by 62 (4.2%) subjects who received NVX-CoV2373, and by 41 (5.5%) subjects who received placebo. Lymphadenopathy was reported more frequently for NVX-CoV2373 recipients (n=11 [0.7%]) than placebo recipients (n=0). Unsolicited AEs that were assessed as related by the investigator were reported for 44 (3.0%) subjects who received NVX-CoV2373 and for 9 (1.2%) subjects who received placebo. Most AEs were mild or moderate in severity, with 0.5% of NVX-CoV2373 recipients and 0.8% of placebo recipients experiencing severe AEs. SAEs were reported by 7 (0.5%) subjects who received NVX-CoV2373, and by 2 (0.3%) subjects who received placebo. Among these, there was one SAE of seizure, which occurred on Day 38 after the second dose of NVX-CoV2373 and was assessed as not related to the investigational product by the investigator. There were no SAEs that were assessed as related to the study product by the investigator. The median follow-up duration time during the Initial Vaccination Period was 2.3 months (range 0.1 - 14.2 months).

During the Crossover Vaccination Period, unsolicited AEs were reported by 163 (24.5%) who crossed over to NVX-CoV2373 from placebo and by 242 (17.9%) subjects crossed over from NVX-CoV2373 to placebo. The most frequently reported unsolicited AEs within 49 days of the first crossover vaccination were of the SOC of General disorders and administration site conditions - by 76 (11.4%) subjects who crossed over to NVX-CoV2373, and by 49 (3.6%) subjects who crossed over to placebo. The most frequent among these were Pyrexia (in 5.3% vs 1.1%) and chills (in 4.2% vs 1.1%). Unsolicited AEs that were assessed as related by the investigator were reported for 48 (7.2%) subjects who crossed over to NVX-CoV2373 and for 17 (1.3%) subjects who crossed over to placebo. SAEs were reported by 8 (1.2%) subjects who crossed over to NVX-CoV2373, and by 11 (0.8%) subjects who crossed over to placebo. SAEs that were assessed as related by the investigator were reported only for 1 (0.2%) subject who crossed over to NVX-CoV2373. This was an SAE of myocarditis, which occurred on Day 3 in a male subject (15 years of age) after the second dose of NVX-CoV2373. The median follow-up time after the NVX-CoV2373 vaccine during the Crossover Vaccination Period was 7.7 months (range 1.2 - 11.2 months).

Reviewer's comment: Whitin 49 days of vaccination during the Crossover Period, the frequency of unsolicited AEs was higher among the subjects who crossed over to NVX-CoV2373 than among those who crossed over to placebo. These were generally consistent with reactogenicity events. Note that during the Crossover Period, there was no collection of solicited adverse reactions.

During the Booster Period, unsolicited AEs were reported by 96 (6.4%) who received a booster dose of NVX-CoV2373. The most frequently reported unsolicited AEs through

28 days after the booster dose were of the SOC of Infections and Infestations and of Respiratory, thoracic, and mediastinal disorders - by 30 (2.0%) subjects each. Unsolicited AEs that were assessed as related by the investigator were reported by 17 (1.1%) subjects. SAEs were reported by 19 (1.3%) subjects, but none of these were assessed as related by the investigator. The median follow-up time after the NVX-CoV2373 vaccine during the Booster Vaccination Period was 6.6 months (range 0.7 – 7.3 months).

There were no deaths observed in the study as of the data cutoff date.

Table 22. Summary of Unsolicited Adverse Events During the Initial, Crossover, and Booster Vaccination Periods (Safety Analysis Set)

Adverse Event Category	**Initial Period NVX-CoV2373 N = 1487 n (%)**	**Initial Period Placebo N = 745 n (%)**	**Crossover Period NVX-CoV2373 N = 666 n (%)**	**Crossover Period Placebo N = 1354 n (%)**	**Booster NVX-CoV2373 N = 1499 n (%)**
TEAEs within 49 days of fist dose or 28 days of booster	237 (15.9)	123 (16.5)	159 (23.9)	235 (17.4)	96 (6.4)
Unsolicited TEAEs through data cut-off date[1]					
TEAEs	239 (16.1)	124 (16.6)	163 (24.5)	242 (17.9)	113 (7.5)
Severe TEAE	8 (0.5)	6 (0.8)	24 (3.6)	31 (2.3)	25 (1.7)
Related TEAE	44 (3.0)	9 (1.2)	48 (7.2)	17 (1.3)	17 (1.1)
Severe Related TEAE	0	0	1 (0.2)	0	1 (<0.1)
Serious TEAE	7 (0.5)	2 (0.3)	8 (1.2)	11 (0.8)	19 (1.3)
Serious Related TEAE	0	0	1 (0.2)	0	0
TEAE leading to vaccination discontinuation	2 (0.1)	1 (0.1)	1 (0.2)	0	0
Related TEAE leading to vaccination discontinuation	1 (< 0.1)	0	0	0	0
Any TEAE leading to study discontinuation	0	0	0	0	0
MAAE	95 (6.4)	50 (6.7)	49 (7.4)	112 (8.3)	52 (3.5)
Related MAAE	5 (0.3)	3 (0.4)	3 (0.5)	2 (0.1)	3 (0.2)
Serious Related MAAE	0	0	1 (0.2)	0	0
PIMMC (Site Reported)	0	0	0	1 (< 0.1)	0
PIMMC (Protocol Defined)	1 (< 0.1)	0	1 (0.2)	2 (0.1)	0
Related PIMMC (Protocol Defined)	0	0	0	0	0
Related AESI: PIMMC (Site Reported)	0	0	1 (0.2)	0	0
Death	0	0	0	0	0
Follow-up time Median (range) (months) [2]	2.3 (0.1, 14.2)	2.3 (0.1, 14.4)	7.7 (1.2, 11.2)	7.7 (1.0, 11.2)	6.6 (0.7, 7.3)

Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
[1] Within the respective vaccination period.
[2] Follow-up time after the second dose/booster within the respective vaccination period.

Source: Adapted from eSub3 Addendum to 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated January 17, 2025, submitted to STN 125817/0/4, Tables 2 (p. 10), Table 4 (p. 12), Table 6 (p. 14), Table 8 (p. 17), Reviewer's computations.

Reviewer's comment: Please refer to the review by the clinical reviewer for details on the safety analyses and conclusions.

Solicited AEs

Solicited local (pain at the injection site, tenderness, redness, and swelling) and systemic (fever, nausea, vomiting, headache, fatigue, malaise, muscle pain, and joint pain) reactions were collected for 7 days after vaccination during the Initial Vaccination Period and during the Booster Vaccination Period. There were no solicited adverse reactions collected during the Crossover Period. Tables 23 and 24 show the rates of reported solicited adverse reactions by maximum severity.

Local reactions were reported by 65.5% of the participants in the NVX-CoV2373 group and by 28.5% of the participants in the placebo group after Dose 1, by 75.3% of the participants in the NVX-CoV2373 group and by 20.6% of the participants in the placebo group after Dose 2, and by 77.1% after the booster dose (Table 23). Pain/tenderness at the injection site was the most commonly reported reaction after NVX-CoV2373 (65.3% after Dose 1, 75% after Dose 2, and 76.8% after booster). Grade 3 local reactions were reported by 8.5% after Dose 2 and by 13.3% after booster. Additionally, there was 1 (<0.1%) subject who reported Grade 4 local reactions (tenderness) after booster dose.

At least one systemic event was reported by 55.2% of the participants in the NVX-CoV2373 group and by 40.8% of the participants in the placebo group after Dose 1 (Table 24). After Dose 2, 74.5% of the participants in the NVX-CoV2373 group and 28.9% of the participants in the placebo group reported at least one systemic event. After the booster dose, 80.8% of the participants reported at least one systemic event. The most commonly reported systemic events after NVX-CoV2373 were fatigue/malaise (28.9% after Dose 1, 57.9% after Dose 2, and 63.0% after booster), muscle pain (34.0% after Dose 1, 49.1% after Dose 2, and 60.4% after booster) and headache (30.4% after Dose 1, 56.9% after Dose 2, and 62.9% after booster). Grade 3 systemic reactions were reported by 3.6% after Dose 1, by 21.9% after Dose 2, and by 29.9% after booster. Additionally, Grade 4 systemic reactions were reported by 2 (0.1%) subjects after Dose 2 and by 5 (0.4%) subjects after booster dose.

Reviewer's comment: Overall, the rates of solicited adverse reactions after the second dose of NVX-CoV2373 were higher than after the first dose, while the rates after the booster dose were in general similar to or higher than those after the second dose. The rates of Grade 3 and 4 solicited adverse reactions were the highest after the booster dose.

Table 23. Local Injection Site Reactions Within 7 Days After Each Dose by Maximum Severity in the Initial Vaccination Period for Dose 1 and 2, and in the Booster Vaccination Period for booster dose (Safety Analysis Set)

Event	NVX-CoV2373 Dose 1 N =1448 n (%)	Placebo Dose 1 N = 726 n (%)	NVX-CoV2373 Dose 2 N = 1394 n (%)	Placebo Dose 2 N = 686 n (%)	NVX-CoV2373 Booster N = 1256 n (%)
Any local injection site reaction	-	-	-	-	-
Any (Grade ≥ 1)	948 (65.5)	207 (28.5)	1050 (75.3)	141 (20.6)	969 (77.1)
Grade 3	22 (1.5)	4 (0.6)	118 (8.5)	4 (0.6)	167 (13.3)
Grade 4	0	0	0	0	1 (<0.1)
Pain	-	-	-	-	-
Any (Grade ≥ 1)	647 (44.7)	126 (17.4)	850 (61.0)	102 (14.9)	812 (64.6)
Grade 3	10 (0.7)	2 (0.3)	38 (2.7)	3 (0.4)	61 (4.9)
Grade 4	0	0	0	0	0
Tenderness	-	-	-	-	-
Any (Grade ≥ 1)	819 (56.6)	153 (21.1)	909 (65.2)	97 (14.1)	828 (65.9)
Grade 3	16 (1.1)	2 (0.3)	93 (6.7)	1 (0.1)	116 (9.2)
Grade 4	0	0	0	0	1 (<0.1)
Pain/tenderness	-	-	-	-	-
Any (Grade ≥ 1)	945 (65.3)	204 (28.1)	1045 (75.0)	141 (20.6)	964 (76.8)
Grade 3	22 (1.5)	4 (0.6)	108 (7.7)	4 (0.6)	145 (11.5)
Grade 4	0	0	0	0	1 (<0.1)
Erythema (Redness)	-	-	-	-	-
Any (Grade ≥ 1)	15 (1.0)	5 (0.7)	104 (7.5)	0	129 (10.3)
Grade 3	0	0	10 (0.7)	0	29 (2.3)
Grade 4	0	0	0	0	0
Swelling	-	-	-	-	-
Any (Grade ≥ 1)	20 (1.4)	3 (0.4)	111 (8.0)	1 (0.1)	119 (9.5)
Grade 3	0	0	8 (0.6)	0	18 (1.4)
Grade 4	0	0	0	0	0

Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 70, p. 175; Adapted from 2019nCoV-301 Addendum 1.0 to 12-Month Adolescent Clinical Study Report, dated March 6, 2024, Table 18, p. 45, submitted to STN 125817/0/4.

Table 24. Systemic Reactions Within 7 Days After Dose 1, Dose 2 and Booster by Maximum Severity (Safety Analysis Set)

Event	NVX-CoV2373 Dose 1 N =1448 n (%)	Placebo Dose 1 N = 726 n (%)	NVX-CoV2373 Dose 2 N = 1394 n (%)	Placebo Dose 2 N = 686 n (%)	NVX-CoV2373 Booster N = 1256 n (%)
Any systemic AE	-	-	-	-	-
Any (Grade ≥ 1)	799 (55.2)	296 (40.8)	1038 (74.5)	198 (28.9)	1015 (80.8)

Event	NVX-CoV2373 Dose 1 N =1448 n (%)	Placebo Dose 1 N = 726 n (%)	NVX-CoV2373 Dose 2 N = 1394 n (%)	Placebo Dose 2 N = 686 n (%)	NVX-CoV2373 Booster N = 1256 n (%)
Grade 3	52 (3.6)	25 (3.4)	305 (21.9)	23 (3.4)	375 (29.9)
Grade 4	0	0	2 (0.1)	0	5 (0.4)
Fever	-	-	-	-	-
Any (Grade ≥ 1)	9 (0.6)	4 (0.6)	235 (16.9)	1 (0.1)	211 (16.8)
Grade 3	1 (<0.1)	0	31 (2.2)	0	44 (3.5)
Grade 4	0	0	0	0	3 (0.2)
Headache	-	-	-	-	-
Any (Grade ≥ 1)	440 (30.4)	181 (24.9)	793 (56.9)	119 (17.3)	790 (62.9)
Grade 3	13 (0.9)	12 (1.7)	87 (6.2)	14 (2.0)	154 (12.3)
Grade 4	0	0	1 (<0.1)	0	2 (0.2)
Fatigue	-	-	-	-	-
Any (Grade ≥ 1)	350 (24.2)	112 (15.4)	696 (49.9)	100 (14.6)	717 (57.1)
Grade 3	23 (1.6)	9 (1.2)	189 (13.6)	11 (1.6)	216 (17.2)
Grade 4	0	0	0	0	1 (< 0.1)
Malaise	-	-	-	-	-
Any (Grade ≥ 1)	215 (14.8)	67 (9.2)	560 (40.2)	51 (7.4)	566 (45.1)
Grade 3	16 (1.1)	7 (1.0)	126 (9.0)	4 (0.6)	170 (13.5)
Grade 4	0	0	0	0	1 (< 0.1)
Fatigue/malaise	-	-	-	-	-
Any (Grade ≥ 1)	418 (28.9)	142 (19.6)	807 (57.9)	113 (16.5)	791 (63.0)
Grade 3	33 (2.3)	13 (1.8)	225 (16.1)	14 (2.0)	269 (21.4)
Grade 4	0	0	0	0	1 (< 0.1)
Muscle pain (myalgia)	-	-	-	-	-
Any (Grade ≥ 1)	492 (34.0)	114 (15.7)	684 (49.1)	82 (12.0)	758 (60.4)
Grade 3	17 (1.2)	4 (0.6)	104 (7.5)	6 (0.9)	143 (11.4)
Grade 4	0	0	0	0	1 (< 0.1)
Joint pain (arthralgia)	-	-	-	-	-
Any (Grade ≥ 1)	102 (7.0)	35 (4.8)	225 (16.1)	21 (3.1)	275 (21.9)
Grade 3	6 (0.4)	1 (0.1)	40 (2.9)	2 (0.3)	50 (4.0)
Grade 4	0	0	0	0	1 (< 0.1)
Nausea/vomiting	-	-	-	-	-
Any (Grade ≥ 1)	113 (7.8)	56 (7.7)	277 (19.9)	33 (4.8)	296 (23.6)
Grade 3	2 (0.1)	3 (0.4)	14 (1.0)	3 (0.4)	20 (1.6)
Grade 4	0	0	1 (<0.1)	0	0

Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 70, p. 175; Adapted from 2019nCoV-301 Addendum 1.0 to 12-Month

Adolescent Clinical Study Report, dated March 6, 2024, Table 26 (p. 60), Table 29 (p. 66), submitted to STN 125817/0/4.

7. INTEGRATED OVERVIEW OF EFFICACY

There was no integrated analysis of efficacy in this application.

8. INTEGRATED OVERVIEW OF SAFETY

The applicant provided integrated summary of safety as supportive evidence of safety. Here I provide an overview of the safety assessments of SARS-CoV-2 rS in adults.

8.1 Safety Assessment Methods

The safety assessment methods are discussed in Section 6.1.9. Additionally, incidence rates and respective 95% CIs based on the Poisson distribution, that accounted for differences in follow-up times, were provided. Risk differences were calculated as a weighted average of risk differences across individual studies, using Cochran-Mantel-Haenszel (CMH) weights based on the sample sizes of individual studies. The analysis was stratified by study to account for different randomization ratios and other differences between the studies.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The available safety database of recipients of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, Original Wuhan Strain formulation) and the respective placebo recipients in the included studies is shown in Table 25. There was no pooling of safety data for adolescent subjects, as only study 2019nCoV-301 Pediatric Expansion enrolled adolescents. In studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-302, and 2019nCoV-501, the investigational product was produced using a different manufacturing process ((b) (4) scale) than the one used in the rest of the studies ((b) (4) scale).

Table 25. Safety Database –Safety Population

Participants Category	Studies	NVX-CoV2373 n (%)[a]	Placebo n (%)[a]
Adult Participants:	Total:	31479	19879
-	2019nCoV-301 Adults [c,d]	19735	9847
-	2019nCoV-307[e]	824	NA
-	2019nCoV-311 Part 1 (Groups B and D)[e]	334	NA
-	2019nCoV-311 Part 2 (Group G)[e]	251	NA
-	2019nCoV-101 Part 1 (Group C)[b,c]	29	23
-	2019nCoV-101 Part 2 (Groups B and C) [b,c,d]	514	255
-	2019nCoV-501[b,c,d]	2211	2197
-	2019nCoV-302 [b,c]	7581	7557
Adolescent Participants:	Total:	1487	745
-	2019nCoV-301 Adolescents [c,d]	1487	745

[a] From Pre-crossover period for the studies that included a crossover; n as of the study initiation.

[b] The investigational product administered as a primary series was produced using a different manufacturing process ((b) (4) scale).
[c] Evaluated a primary series of 2 doses of NVX-CoV2373, 21 days apart.
[d] Evaluated a homologous booster
[e] Evaluated a heterologous booster.
Source: Adapted from Integrated Summary of Safety Report VV-CLIN-000040 (v1.0), Table 1 (p. 37), submitted to STN 125817/0/4.

There were four analysis sets specified for the Integrated Summary of Safety (ISS) in adults. These were the Primary Analysis Set, Primary ISS Analysis Set, Supportive ISS Analysis Set, and Overall ISS Analysis Set (Table 26). All analysis sets, except for the Primary Analysis Set, included integrated safety data.

Table 26. Integrated Analysis Sets

Integrated Analysis Set	**Clinical Studies**
Primary ISS Analysis Set	2019nCoV-301, 2019nCoV-307, and 2019nCoV-311 (Part 1 and Part 2)
Supportive ISS Analysis Set	2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-302, and 2019nCoV-501
Overall ISS Analysis Set	2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311 (Part 1 and Part 2) and 2019nCoV-501

Source: Integrated Summary of Safety Report VV-CLIN-000040 (v1.0), Table 4 (p. 42), submitted to STN 125817/0/4.

The AEs were summarized separately for each vaccination period (Pre-Crossover Primary Series Vaccination Period, Post-Crossover Primary Series Vaccination Period, Combined Pre- and Post-Crossover Primary Series Vaccination Period, and Homologous/Heterologous Booster Vaccination Period).

Primary Analysis for the Primary Series
The primary safety analyses for adults and for adolescents for the primary series of 2 doses (21 days apart) were based on study 2019nCoV-301 Adults and study 2019nCoV-301 Adolescents, respectively, as these were the only studies that evaluated the safety of NVX-CoV2373 as a primary series using the (b) (4) scale drug substance. Please refer to Sections 6.1.12 and 6.2.12 for these analyses.

Overall Analysis for the Primary Series
An additional analysis for the primary series of NVX-CoV2373 was conducted using the Overall ISS Analysis Set. This was based on studies 2019nCoV-301 Adults, 2019nCoV-101 Part 1 and Part 2, 2019nCoV-302, 2019nCoV-501, which included evaluation of a primary series of NVX-CoV2373 (both (b) (4) scale and (b) (4) scale drug substance).

Primary Analysis for a Homologous/Heterologous Booster Dose
For studies 2019nCoV-307 and 2019nCoV-311 (Part 1 and Part 2), participants were analyzed according to their previous vaccination history before enrollment. For study 2019nCoV-307, only participants who received a primary series of mRNA vaccine with

or without a heterologous booster, specifically Moderna (n = 310) or Pfizer (n = 514), were included.

Overall Analysis for a Homologous/Heterologous Booster Dose
An additional analysis for the homologous/heterologous booster dose in adult participants in the Overall ISS Analysis Set was conducted using safety data from studies 2019nCoV-101 (Part 2), 2019nCoV-301 Adults, 2019nCoV-307, 2019nCoV-311 (Part 1 and Part 2), and 2019nCoV-501.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The primary safety analysis for the primary series (based on the Primary ISS Analysis Set) corresponds to the safety analysis for study 2019nCoV-301 Adults (see Section 6.1). Table 27 shows the demographic characteristics for the primary series in the overall ISS Analysis Set (based on studies 2019nCoV-301 Adults, 2019nCoV-101 Part 1 and Part 2, 2019nCoV-302, 2019nCoV-501). The overall ISS Analysis Set included a total of 49949 subjects, of whom 30070 have received at least one dose of NVX-CoV2373 as a primary series, and 19879 had received placebo. The distribution by age and sex was similar between the NVX-CoV2373 and the placebo groups. There was a small imbalance between the two groups in the proportions of Black or African American race, Hispanic/Latino ethnicity, and country, as a result of the differences in the randomization ratio (1:1 and 2:1) and the countries where the different studies were conducted.

Table 27. Demographic characteristics for the primary series in the overall ISS Analysis Set

Demographic Characteristics	**NVX-CoV2373 N[a] = 30070 n (%)**	**Placebo N[a] = 19879 n (%)**	**Total N[a] = 49949 n (%)**
Age	-	-	-
18 to < 65 years	25292 (84.11)	16421 (82.60)	41713 (83.51)
≥ 65 years	4778 (15.89)	3458 (17.40)	8236 (16.49)
Sex	-	-	-
Male	15785 (52.49)	10343 (52.03)	26128 (52.31)
Female	14285 (47.51)	9536 (47.97)	23821 (47.69)
Race	-	-	-
White	22473 (74.74)	14834 (74.62)	37307 (74.69)
Black or African American	4418 (14.69)	3250 (16.35)	7668 (15.35)
Asian	1124 (3.74)	697 (3.51)	1821 (3.65)
American Indian or Alaska Native	1322 (4.40)	663 (3.34)	1985 (3.97)
Native Hawaiian or Other Pacific Islander	58 (0.19)	13 (0.07)	71 (0.14)
Multiple	424 (1.41)	231 (1.16)	655 (1.31)
Not reported	196 (0.65)	123 (0.62)	319 (0.64)
Other	46 (0.15)	59 (0.30)	105 (0.21)
Missing	9 (0.03)	9 (0.05)	18 (0.04)

Ethnicity	-	-	-
Hispanic/Latino	4464 (14.85)	2263 (11.38)	6727 (13.47)
Not Hispanic/Latino	24825 (82.56)	16888 (84.95)	41713 (83.51)
Not reported	624 (2.08)	583 (2.93)	1207 (2.42)
Unknown	155 (0.52)	143 (0.72)	298 (0.60)
Missing	2 (0.01)	2 (0.01)	4 (0.01)
Country	-	-	-
Australia	295 (0.98)	153 (0.77)	448 (0.90)
Mexico	1176 (3.91)	588 (2.96)	1764 (3.53)
South Africa	2211 (7.35)	2197 (11.05)	4408 (8.83)
United Kingdom	7581 (25.21)	7557 (38.01)	15138 (30.31)
United States	18807 (62.54)	9384 (47.21)	28191 (56.44)

[a] Based on studies 2019nCoV-301 Adults, 2019nCoV-101 Part 1 and Part 2, 2019nCoV-302, and 2019nCoV-501.
Source: Integrated Summary of Safety Report VV-CLIN-000040 (v1.0), Table 23 (p. 67), submitted to STN 125817/0/4.

Table 28 shows the demographic characteristics in the Primary ISS Analysis Set for the homologous/heterologous booster based on studies 2019nCoV-301 Adults (Booster Period), 2019nCoV-307 and 2019nCoV-311 (Part 1 and Part 2).

Table 28. Demographic characteristics of participants who received a homologous/heterologous booster – Primary ISS Analysis Set

-	**Homologous**	**Heterologous**	**Heterologous**	-
Demographic Characteristics	**NVX-CoV2373 N = 13353[a] n (%)**	**NVX-CoV2373 After 2 Prior mRNA Doses N = 409[b] n (%)**	**NVX-CoV2373 After ≥ 3 Prior mRNA Doses N = 1000[c] n (%)**	**Total N = 14762 n (%)**
Age	-	-	-	-
18 to < 65 years	11559 (86.56)	409 (100.00)	990 (99.00)	12958 (87.78)
≥ 65 years	1794 (13.44)	0	10 (1.00)	1804 (12.22)
Gender	-	-	-	-
Male	6763 (50.65)	183 (44.74)	415 (41.50)	7361 (49.86)
Female	6590 (49.35)	226 (55.26)	585 (58.50)	7401 (50.14)
Race	-	-	-	-
White	9585 (71.78)	274 (66.99)	801 (80.10)	10660 (72.21)
Black or African American	1886 (14.12)	96 (23.47)	61 (6.10)	2043 (13.84)
Asian	496 (3.71)	15 (3.67)	96 (9.60)	607 (4.11)
American Indian or Alaska Native	1044 (7.82)	5 (1.22)	0	1049 (7.11)
Native Hawaiian or Other Pacific Islander	30 (0.22)	2 (0.49)	3 (0.30)	35 (0.24)
Multiple	225 (1.69)	0	3 (0.30)	228 (1.54)

Not reported	83 (0.62)	3 (0.73)	6 (0.60)	92 (0.62)
Other	0	14 (3.42)	30 (3.00)	44 (0.30)
Missing	4 (0.03)	0	0	4 (0.03)
Ethnicity	-	-	-	-
Hispanic/Latino	3121 (23.37)	69 (16.87)	74 (7.40)	3264 (22.11)
Not Hispanic/Latino	10195 (76.35)	329 (80.44)	875 (87.50)	11399 (77.22)
Not reported	22 (0.16)	7 (1.71)	30 (3.00)	59 (0.40)
Unknown	14 (0.10)	3 (0.73)	19 (1.90)	36 (0.24)
Missing	1 (0.01)	1 (0.24)	2 (0.20)	4 (0.03)
Country	-	-	-	-
Australia	0	60 (14.67)	525 (52.50)	585 (3.96)
Mexico	978 (7.32)	0	0	978 (6.63)
United States	12375 (92.68)	349 (85.33)	475 (47.50)	13199 (89.41)

[a] Participants in study 2019nCoV-301 Adults who received 1 dose of NVX-CoV2373 in the booster vaccination period.
[b] Included participants previously dosed with 2 doses of Pfizer or Moderna COVID-19 vaccines pre-study in studies 2019nCoV-307 and 2019nCoV-311 (Part 1).
[c] Included participants previously dosed with at least 3 doses of Pfizer or Moderna COVID-19 vaccines pre-study in studies 2019nCoV-307 and 2019nCoV-311 (Part 1 and Part 2).
Source: Integrated Summary of Safety Report VV-CLIN-000040 (v1.0), Table 32 (p. 79), submitted to STN 125817/0/4.

8.4 Safety Results

The safety analyses were descriptive in nature, and no formal hypothesis testing was planned.

The primary safety analysis for the primary series (based on the Primary ISS Analysis Set) corresponds to the safety analysis for study 2019nCoV-301 Adults (see Section 6.1.12). Table 29 shows a summary of the integrated unsolicited AEs for the primary series during the Initial Vaccination Period (pre-crossover) in the Overall ISS and Table 30 shows a summary of the integrated unsolicited AEs for the primary series during the Combined Vaccination Period (pre- and post-crossover) in the Overall ISS.

Overall, during the Pre-Crossover Period, slightly more subjects who received NVX-CoV2373 experienced an AE than those who received only placebo (37.67% versus 34.78% through 28 days after the second dose). This was driven mainly by reactogenicity events. A similar pattern was also observed for the Combined Pre- and Post- Crossover Period. The incidence rates (IRs) per 100 Person-Year (PY) of SAEs between the NVX-CoV2373 and placebo recipients in the Pre-Crossover and in the Combined Periods in the Overall ISS Analysis Set were similar (3.09, 95% CI [2.77, 3.43] versus 2.92, 95% CI [2.53, 3.35]) and (2.93, 95% CI [2.75, 3.13] versus 2.96, 95% CI [2.56, 3.40]). The IRs of SAEs of the SOC Infections and Infestations were the highest in both study vaccine groups (IR per 100 PY 0.73, 95% CI [0.64, 0.83] versus 0.72, 95% CI [0.53, 0.95] for the Combined Period). The respective IRs per 100 PY for SAEs of Cardiac disorders were 0.39, 95% CI [0.32, 0.46] versus 0.36, 95% CI [0.23, 0.53], respectively, for the

Combined Period. An SAE of Myocarditis was experienced by 2 subjects in the vaccine group versus 1 subject in the placebo group. An SAE of Pericarditis was experienced by 2 subjects in the vaccine group. Myopericarditis was experienced by 1 subject in the placebo group. Related SAEs were reported by 7 participants in the vaccine group versus 6 participants in the placebo group during the pre-crossover period. During the Combined Period, related (as assessed by the investigator) SAEs were reported by 17 (IR per 100 PY 0.05, 95% CI [0.03, 0.08]) versus 4 (IR 0.06, 95% CI [0.02, 0.15]) subjects. This included events of the SOC of Nervous system disorders, Cardiac disorders. Cholecystitis acute was reported by 2 participants and was the only SAE assessed as related that was reported by more than 1 participant.

Table 29. Summary of Integrated Unsolicited AEs during the Initial Period – Overall ISS

Participants reporting at least one AE	**Pre-Crossover NVX-CoV2373 N = 30070[a] n (% or IR per 100 PY) 95% CI**	**Pre-Crossover Placebo N = 19879[a] n (% or IR per 100 PY) 95% CI**	**RD (95% CI)[b]**
Total Follow-up time (PY)	11108.1	6890.2	-
Median (range) Follow-up time (months) since first dose	3.4 (0 - 20)	3.4 (0 - 20)	-
SAEs through 28 days post dose 2	128 (0.43) (0.36, 0.51)	91 (0.46) (0.37, 0.56)	-0.06 (-0.18, 0.06)
Unsolicited TEAEs through data cut-off date[2]	-	-	-
SAE	343 (3.09) (2.77, 3.43)	201 (2.92) (2.53, 3.35)	0.03 (-0.49, 0.55)
Related SAE	7 (0.06) (0.03, 0.13)	6 (0.09) (0.03, 0.19)	-0.04 (-0.12, 0.05)
AESI (PIMMCs)	54 (0.49) (0.37, 0.63)	34 (0.49) (0.34, 0.69)	-0.05 (-0.26, 0.16)
Deaths	22 (0.20) (0.12, 0.30)	12 (0.17) (0.09, 0.30)	0.04 (-0.09, 0.17)

Abbreviation: PY = Person-years.
[a] The Overall ISS Analysis Set included participants from Clinical Studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301 (Adult Main Study); 2019nCoV-302, and 2019nCoV-501.
[b] Risk difference and its confidence interval were computed from Mantel-Haenszel Standardized Risk Estimates and 95% normal confidence limits with the stratification by study.
Note: For the Pre-Crossover Primary Series Vaccination Period, the end of follow-up (EOF) was defined as date of first crossover or booster dose, date of last contact, or date of data cutoff for the integrated analysis, whichever was earlier, except for the following scenario: If a participant was unblinded during the study and received another vaccine approved under EUA, the safety follow-up was censored at the day of unblinding, which was the EOF.
Source: Adapted from Integrated Summary of Safety Report VV-CLIN-000040 (v1.0) and Tables submitted to STN 125817/0/4.

Table 30. Summary of Integrated Unsolicited AEs during the Combined Pre- and Post-crossover Period – Overall ISS

Participants reporting at least one AE	**Combined Pre-/Post-Crossover NVX-CoV2373 N = 41002[a,b] n (% or IR per 100 PY) 95% CI**	**Combined Pre-/Post-Crossover Placebo N = 19601[a,b] n (% or IR per 100 PY) 95% CI**	**RD (95% CI)[c]**
Total Follow-up time (PY)	32349.9	6688.183	-
Median (range) Follow-up time (months) since first dose	10.2 (0 - 20)	3.4 (0 - 20)	-
SAEs through 28 days post dose 2	177 (0.43) (0.37, 0.50)	90 (0.46) (0.37, 0.56)	-0.05 (-0.16, 0.07)
Through data cut-off date:	-	-	-
SAE	949 (2.93) (2.75, 3.13)	198 (2.96) (2.56, 3.40)	-0.37 (-0.84, 0.10)
Related SAE	17 (0.05) (0.03, 0.08)	4 (0.06) (0.02, 0.15)	-0.02 (-0.10, 0.07)
AESI (PIMMCs)	118 (0.36) (0.30, 0.44)	36 (0.54) (0.38, 0.75)	-0.26 (-0.45, -0.06)
Deaths	71 (0.22) (0.17, 0.28)	12 (0.18) (0.09, 0.31)	0.05 (-0.07, 0.17)

Abbreviation: PY = Person-years.
[a] The Overall ISS Analysis Set included participants from Clinical Studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301 (Adult Main Study); 2019nCoV-302, and 2019nCoV-501.
[b] The ISS analysis sets for the Combined Pre- and Post-Crossover Primary Series Vaccination Period included all participants who received at least 1 dose of NVX-CoV2373 or received only placebo in the Pre-Crossover Primary Series Vaccination Period. Participants who received only placebo in the Pre-Crossover Primary Series Vaccination Period and at least 1 dose of NVX-CoV2373 in Post-Crossover Primary Series Vaccination Period were included in both groups. The EOF was defined as date of first booster dose, date of last contact, or date of data cutoff for the integrated analysis, whichever was earlier, except for the following scenario: If a participant was unblinded during the study and received another vaccine approved under EUA, the safety follow-up was censored at the day of unblinding, and if a participant who received active vaccine in both the Pre- and Post-Crossover Primary Series Vaccination Periods, the safety follow-up was censored at the date of first active vaccine in post-crossover period, which was the EOF.
[c] Risk difference and its confidence interval were computed from Mantel-Haenszel Standardized Risk Estimates and 95% normal confidence limits with the stratification by study.
Source: Adapted from Integrated Summary of Safety Report VV-CLIN-000040 (v1.0) and Tables submitted to STN 125817/0/4.

The primary safety analysis for the homologous booster corresponds to the safety analysis for study 2019nCoV-301 Adults (see Section 6.1.12). Table 31 shows a summary of the integrated unsolicited AEs for the heterologous booster in the Primary Analysis ISS Set, and for the homologous booster in the Overall ISS Set.

Overall, in the Primary ISS Analysis Set, 3 subjects experienced an SAE after a heterologous booster vaccination with NVX-CoV2373 after a prior vaccination with 2 doses of an mRNA vaccine, and 2 subjects experienced an SAE after a heterologous booster vaccination with NVX-CoV2373 after a prior vaccination with at least 3 doses of

an mRNA vaccine. None of these were considered to be related to the investigational product by the investigator. There were no deaths reported for these 2 groups. In the Overall ISS Analysis Set for the homologous booster, the IR per 100 PY for SAEs was 3.14, 95% CI (2.76, 3.56). SAEs of the SOC of Infections and Infestations were the most frequent with an IR of 0.83 per 100 PY, 95% CI (0.64, 1.06). SAEs in the SOC of Cardiac disorders were reported by 31 subjects corresponding to an IR of 0.4, 95% CI (0.27, 0.56) per 100 PY. SAEs in the SOC of Nervous system disorders were reported by 29 subjects corresponding to an IR of 0.37, 95% CI (0.25, 0.53) per 100 PY. Six subjects experienced a related (as assessed by the investigator) SAE, IR 0.08, 95% CI (0.03, 0.17) per 100 PY. These included events of an acute myocardial infarction, cholecystitis, pulmonary embolism, among others, reported by 1 subject, each. There were 11 deaths after a booster dose reported for the subjects in the Overall ISS.

Table 31. Summary of Integrated Unsolicited AEs during the Booster Period

Participants reporting at least one AE	**Primary ISS Heterologous NVX-CoV2373 (2 Prior mRNA Doses) N = 409 [a] n (IR per 100 PY) 95% CI**	**Primary ISS Heterologous NVX-CoV2373 (≥3 Prior mRNA Doses) N =1000 [b] n (IR per 100 PY) 95% CI**	**Overall ISS Homologous NVX-CoV2373 N = 15536[c] n (IR per 100 PY) 95% CI**
Median (range) Follow-up time (months) since first dose	1.0 (0 - 10)	1.0 (0 - 12)	6.7 (0 - 14)
Total Follow-up time (PY)	65.7	243.6	7797.3
Unsolicited TEAEs through data cut-off date:	-	-	-
SAE	2 (3.05) (0.37, 11.00)	5 (2.05) (0.67, 4.79)	245 (3.14) (2.76, 3.56)
Related SAE	0 (0.00) (NA, 5.62)	0 (0.00) (NA, 1.51)	6 (0.08) (0.03, 0.17)
AESI (PIMMCs)	0 (0.00) (NA, 5.62)	2 (0.82) (0.10, 2.97)	30 (0.38) (0.26, 0.55)
Deaths	0 (0.00) (NA, 5.62)	0 (0.00) (NA, 1.51)	11 (0.14) (0.07, 0.25)

a Includes participants in studies 307 and 311 previously vaccinated with 2 doses of Pfizer or Moderna COVID-19 mRNA vaccines.
b Includes participants in studies 307 and 311 previously vaccinated with at least 3 doses of Pfizer or Moderna COVID-19 mRNA vaccines.
c the Overall ISS Analysis Set was conducted using safety data from studies 2019nCoV-101 (Part 2), 2019nCoV-301 Adults, 2019nCoV-307, 2019nCoV-311 (Part 1 and Part 2), and 2019nCoV-501.
Source: Adapted from Integrated Summary of Safety Report VV-CLIN-000040 (v1.0) and Tables submitted to STN 125817/0/4.

<u>Reviewer's comment:</u> The patterns of safety events after a booster dose are generally consistent with those after the primary series.

8.6 Safety Conclusions

The applicant conducted integrated summary of safety analyses for the primary series, homologous booster dose and heterologous booster dose in adults. Overall, these results were consistent with those from the pivotal study 2019nCoV-301 Adults. Please refer to the review by the clinical reviewer for further details and conclusions on safety.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Results of the ongoing pivotal phase 3 study 2019nCoV-301, entitled "A Phase 3, Randomized, Observer-Blinded, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-COV-2 Recombinant Spike Protein Nanoparticle Vaccine (Sars-CoV-2 rS) with Matrix-M1 Adjuvant in Adult Participants ≥ 18 Years with a Pediatric Expansion in Adolescents (12 to < 18 Years)" are summarized as follows:

- In the Adults portion of this crossover study, a total of 29943 subjects were randomized (2:1 ratio) to receive 2 doses (21 days apart) of NVXCoV2373 (N=19961) or placebo (N=9982) in the pre-crossover period (Initial Vaccination Period). Of the randomized subjects, 19735 received at least 1 dose of NVXCoV2373 and 9847 received placebo pre-crossover. During the blinded Crossover Period, a total of 6416 subjects received at least 1 dose of NVX-CoV2373, and a total of 15298 subjects received only placebo. A total of 13,353 participants received a booster dose of NVX-CoV2373 at least 6 months after completion of their active primary series vaccination.

- The primary efficacy endpoint was derived based on the investigator assessments (including severity and start date) and a PCR test results from a central laboratory during the Initial Vaccination Period. It was defined as the first occurrence of mild, moderate or severe PCR-positive COVID-19 starting during the period of 7 days after the second vaccine dose until the administration of the first blinded crossover dose, the day of booster dose or censoring (due to early termination, death, study completion, major protocol deviation, unblinding, data cutoff), whichever is earlier.

- As of the data cutoff date (August 18, 2022), there were a total of 94 first episode cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 (with onset from at least 7 days after second vaccination) accrued in the PP-EFF Analysis Set in the Initial Vaccination Period. Of these, 18 (all mild) were in the NVX-CoV2373 group and 76 (64 mild, 8 moderate, and 4 severe) were in the placebo group. The resulting VE of NVX-CoV2373 was estimated as 89.55%, 95% CI (82.54%, 93.75%) based on a Poisson regression model. The study success criteria for the primary efficacy objective was met, as the LB of the 95% CI for VE was >30%, and the point estimate of VE was >50%.

- In the PP-EFF Analysis Set during the Initial Vaccination Period, there were 12 cases of moderate or severe COVID-19, all of which were in the placebo group. The resulting VE was 100.00% (95% CI: 84.14%, 100.00%). This analysis also met the success criterion for this endpoint.

- The effectiveness of the booster dose was inferred based on immunogenicity endpoints and testing for noninferiority of the immune response at 28 days after the booster dose, compared to that at 14 days after the second dose of the primary series. The GMTR of neutralizing antibody against the ancestral Wuhan strain was 3.2, 95% CI (2.7, 3.8). The respective SCR difference was -1.8%, 95% CI (-6.1%, 2.3%). Thus, the booster immunogenicity success criteria were met and noninferiority was demonstrated, as the GMTR point estimate was >0.83, the LB of the GMTR 95% CI was >0.67, and the LB of the 95% CI of the SCR difference was >-10%.

- During the Initial Vaccination Period, the median follow-up time was 3.2 months (range 0 – 20 months). Unsolicited TEAEs within 28 days after the second vaccination were reported at similar frequencies between the NVX-CoV2373 and placebo arms (34.5% and 34.8%, respectively). The most frequently reported unsolicited TEAEs for NVX-CoV2373 and placebo recipients were of the SOC of Nervous System Disorders (15.9% versus 17.3%, mainly under the PT of headache [15.1% versus 16.4%]), Respiratory, Thoracic, and Mediastinal Disorders (14.8% versus 15.3%), General Disorders and Administration Site Conditions (11.1% versus 11.4%), Gastrointestinal Disorders (8.6% versus 9.5%), Musculoskeletal and connective tissue disorders (6.7% versus 7.3%), and Infections and Infestations (2.4% and 2.5%). Related (as per the investigator) unsolicited TEAEs within 28 days of the second vaccination were reported more frequently in the NVX-CoV2373 group than in the placebo group (2.4% vs 1.4%, respectively).

- During the Initial Vaccination Period, SAEs were reported for 228 (1.2%) subjects in the NVX-CoV2373 group and for 115 (1.2%) subjects in the placebo group. SAEs were assessed as related to study intervention by the investigator for 6 (< 0.1%) subjects in the NVX-CoV2373 group and for 3 (< 0.1%) subjects in the placebo group. Eighteen participants (11 NVX-CoV2373 and 7 placebo) died during the Initial Vaccination Period. None of the deaths were assessed as related to the study intervention by the investigator, except for one death in the placebo group.

- During the Crossover Period, the median follow-up time was 9 months (range 0 – 16 months). Unsolicited TEAEs were reported at a higher frequency after receipt of NVX-CoV2373 (48.1%) than after receipt of placebo (24.4%) within 28 days of the second vaccination, with a higher frequency of related TEAEs reported also for the NVX-CoV2373 recipients (2.0% vs 0.4%). Note that reactogenicity events were not collected as solicited during the Crossover Period, and thus were captured as unsolicited events for that period. These are also reflected in the

higher rates reported among the participants who received NVX-CoV2373, as the vaccine is reactogenic. Severe TEAEs within 28 days of the second vaccination were reported more frequently for the NVX-CoV2373 recipients (16.0%versus 4.9%). The most frequently reported unsolicited TEAEs for the NVX-CoV2373 and placebo recipients, respectively, were of the SOCs of General Disorders and Administration Site Conditions (33.9% and 9.0%), Nervous System Disorders (26.8% and 10.8%), Respiratory, Thoracic, and Mediastinal Disorders (15.3% and 10.6%), Musculoskeletal and Connective Tissue Disorders (26.0% and 5.4%), and Gastrointestinal Disorders (12.3% and 6.4%). Forty participants (10 who received NVX-CoV2373 and 30 who received placebo) died during the Crossover Period, however, none of the deaths in NVX-CoV2373 recipients were considered to be related to vaccination by the investigator. SAEs were reported for 164 (2.6%) NVX-CoV2373 recipients and for 364 (2.4%) placebo recipients. Note that the participants who received placebo during the Crossover Period were subjected to a potential carryover effect as a result of their vaccination with NVX-CoV2373 in the Initial Vaccination Period. Therefore, comparisons between the two groups in the Crossover Period should be interpreted with caution. Further, the Initial and the Crossover Periods had a different length of follow-up, and therefore comparisons of frequencies between these two periods may be inappropriate.

- During the Booster Period, the median follow-up time was 6.7 months (range 0 – 8 months) after vaccination with a booster dose. Unsolicited TEAEs through 28 days after the booster dose of NVX-CoV2373 were reported for 14.3%. Severe TEAEs were reported for 327 (2.4%) participants. SAEs were reported for 227 (1.7%) participants, with 6 (< 0.1%) reporting treatment-related SAEs. One subject experienced a Guillain-Barre syndrome approximately 3 months after receiving a booster dose, however, it was assessed as not related to study intervention by the investigator. Ten (< 0.1%) participants died during the booster period, and none of these were considered to be related to vaccination by the investigator.
- A total of 4 subjects experienced myocarditis, pericarditis, or myopericarditis during the study. Of these, two subjects (<0.1%) reported myocarditis after vaccination with NVX-CoV2373 (on Day 11 after Dose 1, and on Day 29 after Dose 1, respectively). One subject (<0.1%) experienced myopericarditis at 73 days after the second dose of placebo in the initial vaccination period. Two subjects reported pericarditis (one on Day 29 after Dose 1 of NVX-CoV2373 [together with myocarditis], and one on Day 505 after Dose 2 of NVX-CoV2373, respectively).
- Solicited local reactions (pain at the injection site, tenderness, redness, and swelling) with onset within 7 days after Dose 1 were reported by 57.9% of the participants in the NVX-CoV2373 group and by 21.2% of the participants in the placebo group. The respective reactions after Dose 2 were reported by 74.6% and by 20.5% of the participants in the NVX-CoV2373 and placebo groups. After the booster dose, these were reported by 72.8%. Pain/tenderness at the injection site was the most commonly reported reaction after NVX-CoV2373 (57.7% after Dose 1, 74.4% after Dose 2, and 72.4% after booster).

- Solicited systemic reactions (fever, nausea, vomiting, headache, fatigue, malaise, muscle pain, and joint pain) with onset within 7 days after Dose 1 were reported by 48.2% of the participants in the NVX-CoV2373 group and by 40.8% of the participants in the placebo group. After Dose 2, 69.0% of the participants in the NVX-CoV2373 group and 35.5% of the participants in the placebo group reported at least one systemic reaction. After the booster dose, 69.5% of the participants reported at least one systemic event. The most commonly reported systemic events after NVX-CoV2373 were fatigue/malaise (29.9% after Dose 1, 53.8% after Dose 2, and 55.2% after booster), muscle pain (23.3% after Dose 1, 49.9% after Dose 2, and 51.1% after booster) and headache (25.5% after Dose 1, 44.6% after Dose 2, and 44.3% after booster).
- Overall, the rates of solicited adverse reactions after the second dose were higher than after the first dose, while the rates after the booster dose were, in general, similar to those after the second dose. Grades 3 and 4 solicited adverse reactions occurred more frequently after the booster dose. Please refer to the review by the clinical reviewer (Dr. Charles Line) for details on the safety analyses.

- In the Adolescents portion of the study, a total of 2247 subjects were randomized (2:1 ratio) to receive NVXCoV2373 (N=1491) or placebo (N=756). Of these, 1487 received at least 1 dose of NVXCoV2373 and 745 received placebo pre-crossover (Initial Vaccination Period). During the Crossover Period, a total of 666 subjects received at least 1 dose of NVX-CoV2373, and a total of 1354 subjects received only placebo. A total of 1499 participants received a booster dose of NVX-CoV2373 and were included in the Booster Safety Analysis Set.

- The effectiveness of NVX-CoV-2373 in adolescents was assessed based on an immunobridging strategy that included testing for noninferiority of the immune response following vaccination with two doses (primary series) of NVX-CoV-2373 in adolescents compared to the immune response following vaccination with two doses of NVX-CoV-2373 in young adults (18 -< 26 years of age) from the Adults portion of study 2019nCoV-301. Accordingly, the Day 35 MN assay neutralizing antibody GMTR against the original Wuhan serotype (SARS-CoV-2 S Wild-Type Virus) was 1.5, 95% CI (1.3, 1.7). The respective SCR difference was -0.3%, 95% CI (-1.9%, 1.2%). Thus, the study success criteria for the primary immunogenicity objective for immunobridging in adolescents were met, as the LB of the 95% CI for the GMTR was >0.67, the point estimate of GMTR was >0.82, and the LB of the 95% CI for the SCR difference was >-10%.

- As of the data cutoff date of August 6, 2022, in the descriptive analysis of efficacy in adolescents, there were a total of 20 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after the second vaccination accrued in the PP-EFF Analysis Set during the Initial Vaccination Period. Of these cases, 6 were in the NVX-CoV2373 group and 14 were in the placebo group. In the NVX-CoV2373 group, all 6 cases were mild in severity, while in the placebo group, 13 cases were mild and 1 was moderate. The resulting VE of NVX-CoV2373 against PCR-confirmed symptomatic mild,

moderate, or severe COVID-19 with onset from at least 7 days after second vaccination was estimated as 79.82% (95% CI: 47.55%, 92.24%).

- The effectiveness of the booster dose in adolescents was inferred based on immunogenicity endpoints and testing for noninferiority of the immune response at 28 days after the booster dose, compared to that at 14 days after the second dose of the primary series in 56 subjects in the Booster PP-IMM Analysis Set. The respective neutralizing antibody response (MN50) GMTR against the ancestral Wuhan strain was 2.8, 95% CI (2.1, 3.8). The respective SCR difference was 0, 95% CI (-6.4%, 6.4%). Thus, the booster immunogenicity success criteria were met and noninferiority was demonstrated, as the GMTR point estimate was >0.83, the LB of the GMTR 95% CI was >0.67, and the LB of the 95% CI of the SCR difference was >-10%.

- During the Initial Vaccination Period, the rates of unsolicited AEs were similar between the two groups (16.1% versus 16.6%). The most frequently reported unsolicited AEs within 49 days of the first vaccination were of the SOC of Infections and Infestations - by 62 (4.2%) subjects who received NVX-CoV2373, and by 41 (5.5%) subjects who received placebo. Lymphadenopathy was reported more frequently for NVX-CoV2373 recipients (n=11 [0.7%]) than placebo recipients (n=0). Unsolicited AEs that were assessed as related by the investigator were reported for 44 (3.0%) subjects who received NVX-CoV2373 and for 9 (1.2%) subjects who received placebo. Most AEs were mild or moderate in severity, with 0.5% of NVX-CoV2373 recipients and 0.8% of placebo recipients experiencing severe AEs. SAEs were reported by 7 (0.5%) subjects who received NVX-CoV2373, and by 2 (0.3%) subjects who received placebo. There were no SAEs that were assessed as related to the study product by the investigator. The median follow-up duration for the Initial Vaccination Period was 2.3 months (range 0.1 - 14.2 months).

- During the Crossover Vaccination Period, unsolicited AEs were reported by 163 (24.5%) subjects who crossed over to NVX-CoV2373 from placebo and by 242 (17.9%) subjects crossed over from NVX-CoV2373 to placebo. The most frequently reported unsolicited AEs within 49 days of the first crossover vaccination were of the SOC of General disorders and administration site conditions - by 76 (11.4%) subjects who crossed over to NVX-CoV2373, and by 49 (3.6%) subjects who crossed over to placebo. The most frequent among these were Pyrexia (in 5.3% vs 1.1%) and chills (in 4.2% vs 1.1%). Unsolicited AEs that were assessed as related by the investigator were reported for 48 (7.2%) subjects who crossed over to NVX-CoV2373 and for 17 (1.3%) subjects who crossed over to placebo. SAEs were reported by 8 (1.2%) subjects who crossed over to NVX-CoV2373, and by 11 (0.8%) subjects who crossed over to placebo. SAEs that were assessed as related by the investigator were reported only for 1 (0.2%) subject who crossed over to NVX-CoV2373. This was an SAE of myocarditis, which occurred on Day 3 in a male subject (15 years of age) after the second dose of NVX-CoV2373. The median follow-up time after the NVX-

CoV2373 vaccine during the Crossover Vaccination Period was 7.7 months (range 1.2 - 11.2 months).

- During the Booster Period, unsolicited AEs were reported by 96 (6.4%) who received a booster dose of NVX-CoV2373. The most frequently reported unsolicited AEs through 28 days after the booster dose were of the SOC of Infections and Infestations and of Respiratory, thoracic, and mediastinal disorders - by 30 (2.0%) subjects each. Unsolicited AEs that were assessed as related by the investigator were reported by 17 (1.1%) subjects. SAEs were reported by 19 (1.3%) subjects, but none of these were assessed as related by the investigator. The median follow-up time after the NVX-CoV2373 vaccine during the Booster Vaccination Period was 6.6 months (range 0.7 – 7.3 months). There were no deaths observed in the study in adolescents as of the data cutoff date.
- The applicant conducted integrated summary of safety analyses for the primary series, homologous booster dose and heterologous booster dose in adults. Overall, these results were consistent with those from the pivotal study 2019nCoV-301 Adults. Please refer to the review by the clinical reviewer for further details and conclusions on safety.

- The statistical methods used by the applicant were generally appropriate and consistent with those prespecified in the study protocol and in the SAP. The main results were verified based on data submitted in the SDTM format.

10.2 Conclusions and Recommendations

In conclusion, the primary efficacy objective for the Adults portion of the pivotal study 2019nCoV-301 was met and the safety profile of the NVX-CoV-2373 vaccine as of the data cutoff date was described. The safety analyses were descriptive in nature and the study was not powered for formal hypothesis testing between the study arms with regard to safety. I defer to the clinical reviewer whether the observed numerical imbalance for myocarditis and/or pericarditis, and for cardiomyopathy related safety events between the study arms is of clinical significance and whether further investigation for these events in the post-marketing setting is to be recommended. The study demonstrated that the NVX-CoV-2373 vaccine (administered as a two dose [21 days apart] primary series regimen) is efficacious against the primary efficacy endpoint of mild, moderate or severe COVID-19 in adults 18 years of age or older. The effectiveness of a booster dose, administered at least 5 months after the second dose, was inferred based on demonstrating noninferiority of the immune response at 28 days after the booster compared to that at 14 days after the second dose of the primary series. The effectiveness of the primary series of NVX-CoV-2373 vaccine (two doses, 21 days apart) in adolescents was inferred based on an immunobridging strategy. Specifically, it was demonstrated that the immune response at 14 days after the second dose of NVX-CoV-2373 in adolescents was noninferior to that in young adults (18 -< 26 years of age) from the Adults portion of study 2019nCoV-301. The effectiveness of a booster dose in adolescents, administered at least 6 months after the second dose, was inferred based on demonstrating noninferiority of the immune response at 28 days after the booster compared to the immune response at 14 days after the second dose of the primary series. No specific safety patterns for adolescents were

identified in addition to the reactogenicity events. The effectiveness and safety of the strain-updated vaccine and of the single dose regimen are inferred based on the results of studies 2019nCoV-311 and 2019nCoV-313. Please refer to the review by Dr. Kumaresh Dhara for specific details and conclusions for these studies.