Application Type	Original BLA
STN	125817/0
CBER Received Date	April 1, 2024
PDUFA Goal Date	April 1, 2025
(b) (6)	
	(b) (6)
Priority Review	No
Reviewer Name(s)	(b) (6)
Review Completion Date / Stamped Date	
Concurrence	(b) (6)
	(b) (6)
	(b) (6)
Applicant	Novavax, Inc.
Established Name	COVID-19 Vaccine, Adjuvanted
(Proposed) Trade Name	Nuvaxovid
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	5 µg SARS-CoV2 rS with 50 µg Matrix-M adjuvant
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular injection
Dosing Regimen	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 (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
ANCOVA	Analysis of Covariance
Anti-N	Anti-nucleocapsid
BLA	Biologics License Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
ELISA	Enzyme-Linked Immunosorbent Assay
EoS	End of Study
EU/mL	ELISA units per ML
EUA	Emergency Use authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMEU	Geometric Mean ELISA UNIT
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
hACE2	Human angiotensin-converting enzyme 2
ICCS	Intracellular cytokine staining
IgG	Immunoglobulin G
IL-2	Interleukin-2
IM	Intramuscular
LB	Lower Bound
LLOQ	Lower Limit of Quantification
MAAE	Medically Attended Adverse Event
MN_{50}	Microneutralization Assay with inhibitory dilution concentration of 50%
mRNA	Messenger Ribonucleic Acid
NAb	Neutralizing Antibody
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PIMMC	Potential immune-mediated medical conditions
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SRR	Seroresponse Rates
TEAE	Treatment-Emergent Adverse Event

1. Executive Summary

Nuvaxovid is an adjuvanted, protein-based coronavirus disease 2019 (COVID-19) vaccine authorized for emergency use in individuals aged 12 years and older as primary series vaccination and for booster vaccination. Nuvaxovid comprises the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) (5 µg per dose) and Matrix-M^{TM} adjuvant (50 µg per dose). Novavax submitted this Biologics License Application (BLA) for licensure of Nuvaxovid for active immunization to prevent coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in individuals 12 years of age and older. Nuvaxovid is intended for intramuscular (IM) administration (0.5 mL) on Days 0 and 21 (+ 7 days) for primary vaccination series and, at least 6 months thereafter, for homologous or heterologous boosting vaccination in adults.

This statistical review memo covers clinical studies 2019nCoV-311 Part 1 (311 Part 1), 2019nCoV-311 Part 2 (311 Part 2), and 2019nCoV-313 Part 2 (313 Part 2). The Nuvaxovid vaccines investigated in these studies include monovalent and bivalent NVX-CoV2373 (prototype), NVX-CoV2515 (Omicron BA.1 strain), NVX-CoV2540 (Omicron BA.5 strain) and NVX-CoV2601 (Omicron XBB.1.5 strain). Please refer to the statistical review memo by (b) (6) regarding the review of the pivotal efficacy study 2019nCoV-301 submitted to the BLA.

Study 311 was a two-part, phase 3, randomized, observer-blind study to evaluate the safety and immunogenicity of omicron subvariant and bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines. This study provided evidence to support the use of Nuvaxovid as a heterologous booster.

Study 311 Part 1 evaluated a single booster dose of monovalent NVX-CoV2515 (SARS-CoV-2 BA.1 [Omicron] subvariant), monovalent NVX-CoV2373 (Wuhan-Hu-1), and bivalent prototype and Omicron subvariant vaccine (site mixed NVX-CoV2373 and NVX-CoV2515) in previously vaccinated adults 18 to 64 years of age (inclusive) in Australia. In this study, 122 subjects who previously received 2 doses of Moderna and/or Pfizer-BioNTech COVID-19 prototype COVID-19 vaccines ≥ 180 days ago were randomized 1:1 to receive 1 dose of NVX-CoV2515 (Group A) or NVX-CoV2373 (Group B). This study also enrolled and randomized subjects who had previously received 3 doses of Moderna and/or Pfizer BioNTech COVID-19 vaccines ≥ 90 days before enrolment to receive 1 dose of NVX-CoV2515 (Group C), NVX-2373 (Group D) or bivalent NVX-CoV2373+NVX-CoV2515 (Group E). Of note, 286, 274 and 269 participants received NVX-CoV2515 (Group C), NVX-2373 (Group D), or bivalent NVX-CoV2373+NVX-CoV2515 (Group E), respectively.

The primary objective of Study 311 Part 1 was to determine whether NVX-CoV2515 (Group C) induced superior antibody responses to the Omicron BA.1 subvariant compared to the antibody responses induced by NVX-CoV2373 (Group D) in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

The geometric mean microneutralization (MN50) titers at Day 14 were 130.8 (95% CI: 109.2, 156.7) vs. 83.9 (95% CI: 69.6, 101.2) for NVX-CoV2515 and NVX-CoV2373, respectively, resulting in an adjusted Geometric Mean Titer Ratio (GMTR) of 1.6 (95% CI: 1.33, 2.03), meeting the superiority success criterion of the LB of the two-sided 95% CI being >1. Seroresponse rates (SRRs) were 73.4% (95% CI: 64.7%, 80.9%), versus 50.9% (95% CI: 41.4%, 60.3%), in NVX-CoV2515 and NVX-CoV2373 groups, respectively, resulting in a difference of 22.5% (95% CI: 10.3%, 34.2%) in SRRs, meeting the success criterion of the LB of the 95% CI being > -5%.

The safety and reactogenicity profiles of the treatment groups were generally similar. Of note, 1(1.6%), 2 (3.3%), 8 (2.8%), 4 (1.5%) and 4 (1.5%) participants reported serious adverse events (SAEs) till the end of the study in Groups A, B, C, D and E, respectively. All SAEs (including fatalities) reported in this study were assessed by the investigator as not causally related to vaccination.

Study 311 Part 2 evaluated the safety and immunogenicity of two booster doses of monovalent NVX-CoV2540 (SARS-CoV-2 BA.5 [Omicron] subvariant), monovalent NVX-CoV2373 (Wuhan-Hu-1), and bivalent prototype and Omicron BA.5 subvariant vaccine (site mixed NVX-CoV2373 and NVX-CoV2540) in previously vaccinated adults 18 years of age or older in Australia. In this study, participants who were previously vaccinated with ≥ 3 doses of Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days ago were planned to be randomized to receive NVX-CoV2540 (Group F), NVX-CoV2373 (Group G) or NVX-CoV2373+NVX-CoV2540 (Group H). The subjects enrolled in these groups were planned to receive two doses of the same vaccine at Day 0 and Day 90. The primary objective of the study was to evaluate whether the bivalent vaccine (NVX-CoV2373+NVX-CoV2540) induced superior antibody responses compared to the antibody response induced by NVX-CoV2373. The coprimary endpoints included the Neutralization antibody (NAb) Titers and SRRs in NAb titers to the Omicron BA.5 subvariant and NAb titers to the ancestral (Wuhan) strain assessed at Day 28 post first booster dose.

The success criteria for all 3 co-primary endpoints were achieved in Part 2 of the study. Briefly, the bivalent vaccine induced a superior NAb response against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 with GMTs of 1100.9 (95% CI: 913.9, 1326.1) vs. 586.7 (95% CI: 480.9, 715.8) at Day 28, resulting in an adjusted GMTR of 2.0 (95% CI: 1.72, 2.37) where the lower bound (LB) of the two-sided 95% CI was > 1, meeting the superiority criterion. In addition, the bivalent vaccine induced a non-inferior SRR against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 (40.4% [95% CI: 34.1%, 47.0%] vs. 12.3% [95% CI: 8.3% 17.3%], respectively) at Day 28, with a difference in SRRs of 28.1% (95% CI: 20.5%, 35.6%) where the LB of the two-sided 95% CI was > -5%, meeting the non-inferiority criterion. Lastly, the bivalent vaccine induced a non-inferior response versus NVX-CoV2373 in regard to the induction of NAbs against the ancestral (Wuhan) pseudovirus (GMTs 2230.9 [95% CI: 2007.1, 2707.0] versus 2361.1 [95% CI: 2031.1, 2744.7], respectively) at Day 28, with an adjusted GMTR

of 1.0 (95% CI: 0.84, 1.18) where the LB of the two-sided 95% CI was > 0.67, meeting the non-inferiority criterion.

The safety and reactogenicity profiles of the treatment groups were generally similar. One (0.4%) participant in the bivalent vaccine group reported a Grade 4 solicited systemic adverse event (AE) (fatigue/malaise). From the first vaccination until the data cutoff date of November 22, 2023, 7 (2.8%), 10 (4.0%) and 3 (0.8%) participants in Groups F, G and H, respectively, reported SAEs. One participant had a related serious adverse event (SAE) of fourth nerve paralysis that occurred after the initial vaccination of NVX-CoV2540 (Group F) and did not receive the second booster dose.

Study 313 was a two-part, Phase 2/3, Open-Label study to evaluate the safety and immunogenicity of a single dose of XBB.1.5 (Omicron subvariant), NVX-CoV2601 vaccine in previously mRNA COVID-19 vaccinated and baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants aged 18 years and older in the U.S.

In Study 313 Part 1, 332 participants who were previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer/BioNTech prototype monovalent and/or BA.4/5-containing bivalent COVID-19 vaccines with the last dose administered ≥ 90 days prior to study vaccination were administered with NVX-CoV2601 vaccine. The primary objective of this part of the study was to determine if the NVX-CoV2601 booster vaccine induced superior antibody responses to the XBB.1.5 subvariant compared to those of a historical control from clinical Study 311 Part 2 who received NVX-CoV2373 (Group G). Study 313 Part 1 met the success criteria for the primary objective. Study 313 Part 1 was not reviewed separately in this memo as it does not provide effectiveness data to support the licensure of Nuvaxovid.

Study 313 Part 2 enrolled vaccine naïve participants (participants who were unvaccinated to SARS-CoV-2) with a clinical history of COVID-19-like illness. In this part of the study 338 participants received one dose of NVX-CoV2601 vaccine. The primary objective of the study was to evaluate whether a single dose of NVX-CoV2601 vaccine in vaccine naïve participants induced noninferior antibody responses and SRRs to the Omicron XBB.1.5 subvariant compared to the historical control of subjects who were enrolled in Study 313 Part 1. This statistical review focuses on Part 2 of the study as it provided data to support the use of Nuvaxovid in vaccine naïve participants with evidence of prior SARS-CoV-2 infection.

The geometric mean nAb titers against Omicron XBB.1.5 pseudovirus following a single dose of NVX-2601 were 1303.7 (95% CI: 1087.4, 1563.0) and 955.5 (95% CI: 814.0, 1121.4) in vaccine naïve and previously vaccinated participants, respectively, resulting in an adjusted GMTR of 1.8 (95% CI: 1.4, 2.2), meeting the noninferiority success criterion of the LB of the two-sided 95% of GMTR being > 0.67. The SRRs were 74.3% (95% CI: 68.9%, 79.3%) and 64.3% (95% CI: 58.6%, 69.6%) in vaccine naïve and previously vaccinated participants, respectively, resulting in a difference in SRRs of 10% (95% CI: 2.6%, 17.4%), meeting the noninferiority criterion of the LB of the 95% CI being >-10%.

The safety and reactogenicity profiles were generally similar in both vaccine naïve and previously vaccinated groups. Of note, 5 (1.5%) and 4 (1.2%) of the participants in vaccine naïve and previously vaccinated groups reported SAEs. None of these SAEs were assessed as related to the study vaccination by the investigator.

There were no cases of myocarditis/pericarditis reported in Studies 311 Part 1, 311 Part 2, 313 Part 1 and 313 Part 2.

I have verified the key study results based on the submitted datasets.

In summary, Study 311 Part 1 demonstrated that NVX-CoV2515 induced superior immune response to NVX-CoV2373 among subjects who previously received ≥ 3 doses of mRNA COVID-19 vaccines. Study 311 Part 2 demonstrated that Bivalent NVX-CoV2373+NVX-CoV2540 induced superior NAb response to NVX-CoV2373 against Omicron BA.5 subvariant pseudovirus, and induced noninferior NAb response to NVX-CoV2373 against Wuhan strain among subjects who previously received ≥ 3 doses of mRNA COVID-19 vaccines. Study 313 Part 2 demonstrated that a single dose of NVX-CoV2601 induced noninferior immune response in SARS-CoV-2 seropositive, vaccine naïve participants compared to subjects who previously received at least 3 doses of mRNA COVID-19 vaccines. I defer to the clinical reviewers regarding the overall assessment of safety and the final regulatory action for this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is an adjuvanted nanoparticle vaccine that contains full-length recombinant SARS-CoV-2 spike protein based on the ancestral (Wuhan) strain, stabilized in its pre-fusion conformation, and produced from baculovirus infected Sf9 (fall armyworm) insect cells. The vaccine contains Matrix-M adjuvant.

Novavax COVID-19 Vaccine, Adjuvanted was authorized for the prevention of COVID-19 for individuals 18 years of age older (2-dose series in unvaccinated individuals) on July 13, 2022. The authorization was extended to include individuals aged 12 through 17 years on August 19, 2022. On October 19, 2022, Novavax COVID-19 vaccine was authorized as a first booster dose (0.5 mL) to individuals aged 18 years and older, at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine. Novavax COVID-19 vaccine, Adjuvanted (2023-2024 formula) was authorized in individuals 12 years of age and older on October 3, 2023. On August 30, 2024, Novavax COVID-19 vaccine, Adjuvanted (2024-2025 formulation was authorized to prevent COVID-19 in individuals 12 years of age and older (in pre-filled syringes). Please refer to the clinical review memo regarding the details of the authorizations at different timepoints and the populations the corresponding vaccine was authorized for.

Novavax submitted this original Biologics License Application (BLA) to seek licensure of Nuvaxovid for the active immunization to prevent coronavirus 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in individuals 12 years of age and older. This 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-302 (Wuhan formulation), 2019nCoV-501 (Wuhan formulation), 2019nCoV-307 (Wuhan formulation), 2019nCoV-313 (Part 2-Omicron XBB.1.5 formulation). This review memo focuses on studies 2019nCoV 311 (Parts 1 and 2) and 2019nCoV-313 Part 2.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

No significant issues were identified.

3.2 Compliance With Good Clinical Practices And Data Integrity

No substantial issues were found during the review of this BLA.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to review memos from other review disciplines.

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

5.1 Review Strategy

This statistical review focuses on the clinical safety and immunogenicity data collected in Phase III studies 2019nCoV2-311 Part 1 (Final Clinical Study Report [CSR]), 2019nCoV2-311 Part 2 (Day 189 CSR), and 2019nCoV2-313 Part 2 (Final CSR).

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

125817/0.4 (Submitted on April 1, 2024)
Module 5: Datasets and Clinical Study Report for Study 311 Part 1

125817/0.15 (Submitted on April 29, 2024)

Module 5: Datasets and Clinical Study report for Study 311 Part 2

125817/0.45 (Submitted on November 15, 2024)
Module 5: Datasets and Clinical Study report for Study 313 Part 2

125817/0.48 (Submitted on December 4, 2024)
Module 5: Partial set of Datasets for Study 313 Part 1

125817/0.50 (Submitted on December 9, 2024)
Module 5: Complete set of Datasets for Study 313 Part 1

125817/0.54 (Submitted on December 17, 2024)
Module 1: Meeting Minutes from CBER-Novavax December 6, 2024, meeting regarding BLA IR #27 and Clinical Datasets

125817/0.56 (Submitted on December 20, 2024)
Module 1: Minutes from Late Cycle Review Meeting, December 17, 2024.

125817/0.57 (Submitted on December 23, 2024)
Module 1: Response to Information Request Sent on October 11, 2024.

125817/0.62 (Submitted on January 9, 2025)
Module 5: Updated datasets for Studies 311 Part 1 and 311 Part 2

125817/0.64 (Submitted on January 24, 2025)
Module 1.14.1: Draft Labeling
Module 5: Updated Immunogenicity tables for Studies 311 Part 1 and 311 Part 2.

125817/0.89 (Submitted on March 11, 2025)
Module 1.11.3: Clinical Information Amendment
Response to information request (IR) regarding patient listings for unsolicited AEs for studies 311 Part 1, 311 Part 2, 313 Part 1, and 313 Part 2.

125817/0.95 (Submitted on March 18, 2025)
Module 1.14.3: Draft Labeling

125817/0.98 (Submitted on March 19, 2025)
Module 1.11.3: Clinical Information Amendment
Response to follow-up IR regarding patient listings for Study 313 Part 1

125817/0.100 (Submitted on March 21, 2025)
Module 1.11.3: Clinical Information Amendment regarding median date calculation for booster doses for Study 311 Part 2

5.3 Table of Studies/Clinical Trials

Please refer to the statistical review memo by (b) (6) regarding a full list of clinical studies submitted to this BLA. The clinical studies reviewed in this review memo are summarized in Table 1.

Table 1: Clinical Study reviewed to support the BLA.

Study	N	Age	Description
2019nCoV-311 (Part 1)	953	18-64 years	Part 1 of A Multi-Part, Phase 3, Randomized, Observer Blinded Study to Evaluate and Compare the Safety and Immunogenicity of Monovalent NVX-CoV2373 (Wuhan-Hu-1), Monovalent NVX-CoV2515 (Omicron BA.5 Subvariant) and Bivalent SARS-CoV-2 rS Vaccine (NVX-CoV2373+NVX-CoV2515)in Adults Previously Vaccinated with Other COVID-19 Vaccines
2019nCoV-311 (Part 2)	1002	≥ 18 years	Part 2 of A Multi-Part, Phase 3, Randomized, Observer Blinded Study to Evaluate and Compare the Safety and Immunogenicity of Monovalent NVX-CoV2373 (Wuhan-Hu-1), Monovalent NVX-CoV2540 (Omicron BA.5 Subvariant) and Bivalent SARS-CoV-2 rS Vaccine (NVX-CoV2373+NVX-CoV2540) in Adults Previously Vaccinated with Other COVID-19 Vaccines
2019nCoV-313 Part 2	338	≥ 18 years	Part 2 of a 2-part, Phase 2/3, open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 in adult participants ≥ 18 years of age previously vaccinated with messenger ribonucleic acid (mRNA) COVID-19 vaccine (Part 1) and of a single dose of NVX-CoV2601 in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve adult participants ≥ 18 years of age (Part 2) in the U.S. and its territories.

Source: Summarized by reviewer.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 2019nCoV-311 Part 1

Title of Study 2019nCoV-311: A Multi-Part, Phase 3, Randomized, Observer Blinded Study to Evaluate the Safety and Immunogenicity of Omicron Subvariant and Bivalent SARS-CoV-2 rS Vaccines in Adults Previously Vaccinated with Other COVID-19 Vaccines

6.1.1 Objectives

Primary Objective

1. To determine if NVX-CoV2515 induces superior antibody responses to the Omicron BA.1 subvariant compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

Secondary Objectives

1. To assess neutralizing antibodies to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 viruses induced by NVXCoV2515 compared to the antibody response induced by NVX-CoV2373 over time in participants previously vaccinated with 2 or 3 doses of the Moderna and/or Pfizer- BioNTech prototype vaccines.

2. To assess immunoglobulin G (IgG) antibody levels generated against the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 strains in participants previously vaccinated with 2 or 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

3. To assess antibody responses in a human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition assay to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 strains in participants previously vaccinated with 2 or 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

4. To determine if the bivalent vaccine (NVX-CoV2373 +NVX-CoV2515) induces noninferior antibody responses to the ancestral (Wuhan) strain compared to the antibody response induced by NVXCoV2373 in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

5. To determine if the bivalent vaccine (NVX-CoV2373 + NVX-CoV2515) induces noninferior antibody responses to the Omicron BA.1 variant compared to the antibody response induced by NVXCoV2515 in participants previously

vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

6. To assess neutralizing antibodies induced by the bivalent vaccine (NVX-CoV2373 + NVXCoV2515) to the ancestral (Wuhan) and Omicron BA.1 viruses over time in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

7. To assess IgG antibody levels induced by the bivalent vaccine (NVX-CoV2373 + NVXCoV2515) in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

8. To assess antibody responses in a hACE2 receptor binding inhibition assay induced by the bivalent vaccines (NVX-CoV2373 + NVXCoV2515) to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 strains in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

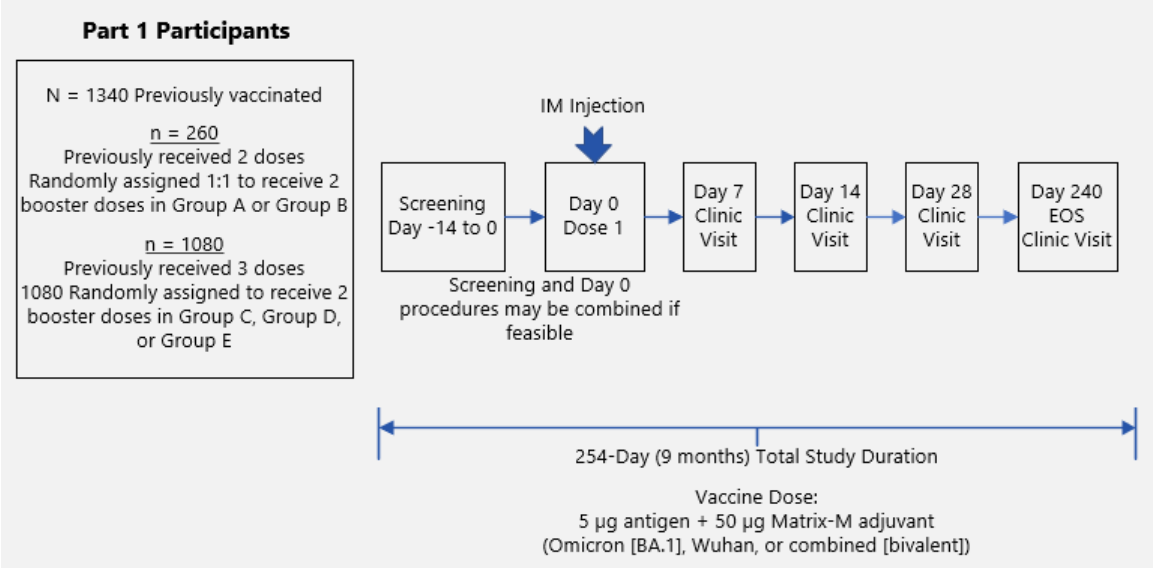
9. To assess the overall safety of 1-booster dose regimens containing NVX-CoV2515, NVX-CoV2373, or the bivalent (NVX-CoV2373 + NVXCoV2515) vaccine in participants previously vaccinated with 2 or 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

6.1.2 Design Overview

Study 2019nCoV-311 (Part 1) was initiated on May 31, 2022 (first participant screened). As per the applicant, enrollment was completed on July 17, 2022.

Study 2019nCoV-311 was a two-part, Phase 3, randomized, observer-blinded study evaluating the safety and immunogenicity of Omicron subvariant vaccines in previously vaccinated adults. Part 1 evaluated a single booster dose of the Omicron BA.1 subvariant vaccine (NVX-CoV2515) and the prototype Novavax vaccine (NVX-CoV2373) alone and bivalent prototype and Omicron subvariant vaccines (NVX-CoV2373 + NVX-CoV2515) in adults 18 to 64 years of age (inclusive) who previously received 2 doses of the Moderna and/or Pfizer- BioNTech prototype vaccines ≥ 180 days prior to study vaccination or 3 doses of the Moderna and/or Pfizer /BioNTech prototype vaccines ≥ 90 days prior to study vaccination. Approximately 1,340 medically stable adult participants were to be enrolled in Part 1 (as shown in Figure 1).

Figure 1: Study Design of Study 311 Part 1



Abbreviations: EOS = end of study; IM = intramuscular.

Note: Group A = NVX-CoV2515; Group B = NVX-CoV2373; Group C = NVX-CoV2515; Group D = NVX-CoV2373; Group E = NVX-CoV2373 + NVX-CoV2515.

Source: Figure 1 of Clinical Study Protocol for Study 2019nCoV-311 submitted to BLA 125817/0.4.

Approximately 260 participants who previously received 2 doses of Moderna and/or Pfizer-BioNTech COVID-19 prototype COVID-19 vaccines ≥ 180 days before dosing with investigational treatment were to be randomized 1:1 to Group A or Group B:

- **Group A: 1 Dose of NVX-CoV2515 (5 µg)** - Coformulated Omicron BA.1 SARS CoV-2 rS vaccine with Matrix-M adjuvant.
- **Group B: 1 Dose of NVX-CoV2373 (5 µg) -** Coformulated prototype SARS-CoV-2 rS vaccine with Matrix-M adjuvant, i.e., Novavax COVID-19 vaccine, Adjuvanted (Original Monovalent) vaccine.

Additionally, approximately 1,080 participants who previously received 3 doses of the Moderna and/or Pfizer-BioNTech COVID-19 prototype COVID-19 vaccines ≥ 90 days before dosing were to be randomized 1:1:1 to Group C, Group D, or Group E:

- **Group C: 1 Dose of NVX-CoV2515 (5 µg)** - Coformulated Omicron BA.1 SARS CoV-2 rS vaccine with Matrix-M adjuvant.
- **Group D: 1 Dose of NVX-CoV2373 (5 µg)** - Coformulated prototype SARS-CoV-2 rS vaccine with Matrix-M adjuvant, i.e., Novavax COVID-19 vaccine, Adjuvanted (Original Monovalent) vaccine.
- **Group E: 1 Dose of bivalent NVX-CoV2373 + NVX-CoV2515 (5 µg total)** - Prototype/BA.1 Bivalent Vaccine coformulated with Matrix-M adjuvant.

In Part 1, blood samples for immunogenicity assessments were collected and analyzed before vaccination on Day 0 and on Days 7, 14, and 28.

Safety assessments included collection of solicited (local and systemic reactogenicity events) through 7 days after vaccination through e-Diaries, unsolicited treatment-emergent adverse events (TEAEs) from Day 0 (post-vaccination) through Day 28, medically attended adverse events (MAAEs) and adverse events of special interest (AESIs) from Day 0 through Day 240, and serious adverse events (SAEs) from screening through Day 240.

6.1.3 Population

Male and nonpregnant female Participants ≥ 18 and ≤ 64 years of age who were medically stable and previously received 2 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines ≥ 180 days or 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines ≥ 90 days prior to study vaccination.

6.1.4 Study Treatments or Agents Mandated by the Protocol

NVX-CoV2373 (5 μg) is coformulated prototype SARS-CoV-2 rS vaccine with Matrix-M adjuvant: supplied as a solution for preparation for injection, at a concentration of 10 μg antigen and 100 μg adjuvant per mL.

NVX-CoV2515 (5ug) is a coformulated Omicron BA.1 SARS-CoV-2 rS vaccine with Matrix-M adjuvant: supplied as a solution for preparation for injection, at a concentration of 10 ug antigen and 100 ug antigen per mL.

The BA.1 bivalent vaccine (site-mixed NVX-CoV2373 and NVX-CoV2515) contained antigen for the prototype SARS-CoV-2 strain and Omicron BA.1 subvariant, was prepared from study supplies of NVX-CoV2373 and NVX-CoV2515.

6.1.6 Sites and Centers

The study was conducted at 18 study centers by 18 investigators in Australia.

6.1.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

6.1.8 Endpoints and Criteria for Study Success

Co-primary Endpoints:

1. Microneutralization (MN) geometric mean titers (GMTs) with an inhibitory concentration of 50% (MN_{50}) to the Omicron BA.1 subvariant, assessed at Day 14 following initial study vaccination and analyzed by previous vaccine combination received.

2. Seroresponse rates (SRRs)from baseline [Day 0] in MN_{50} titer to the Omicron BA.1 subvariant, assessed at Day 14 following initial study vaccination.
   SRR was defined as the percentage of participants with baseline assay result ≥LLOQ who achieved ≥ 4- fold rise in antibody response from baseline. If the baseline titer was <LLOQ, it was imputed by LLOQ/2.

Secondary Endpoints:

Endpoints for 1st Secondary Objective

- MN_{50} GMTs to the ancestral (Wuhan) and Omicron BA.1 viruses at relevant time points (Days 0, 7, 14, 28, and 240) and analyzed by previous vaccine combination received.

- MN_{50} geometric mean fold rise (GMFR) to the ancestral (Wuhan) and Omicron BA.1 viruses at relevant time points (Days 7, 14, 28, and 240) from baseline (Day 0) and analyzed by previous vaccine combination received.

- SRRs in MN_{50} titer concentrations to the ancestral (Wuhan) and Omicron BA.1viruses at relevant time points (Days 7, 14, 28, and 240) and analyzed by previous vaccine combination received.

Endpoints for 2nd Secondary Objective

- IgG geometric mean concentrations (GMCs, EU/mL) to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 S proteins at relevant time points (Days 0, 7, 14, 28, 240) and analyzed by previous vaccine combination received. Derived/calculated endpoints based on these data will include GMFR and SRRs.

Endpoints for 3rd Secondary Objective

- GMTs to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 viruses at relevant time points (Days 0, 7, 14, 28, 240) and analyzed by previous vaccine combination received. Derived/calculated endpoints based on these data will include GMFR and SRRs.

Endpoints for 4th Secondary Objective

- MN_{50} GMTs to the ancestral (Wuhan) virus, assessed at Day 14 following initial study vaccination and analyzed by previous vaccine combination received.

- MN_{50} GMFRs to the ancestral (Wuhan) virus at Day 14, from baseline (Day 0) and analyzed by previous vaccine combination received.

- SRR in MN_{50} titer concentrations to the ancestral (Wuhan) virus, assessed at Day 14 following initial study vaccination.

Endpoints for 5th Secondary Objective

- MN_{50} GMTs to the Omicron BA.1 subvariant virus, assessed at Day 14 following initial study vaccination and analyzed by previous vaccine combination received.

- MN_{50} GMFRs to the Omicron BA.1 subvariant virus at Day 14, from baseline (Day 0) and analyzed by previous vaccine combination received.

- SRR in MN_{50} titer concentrations to the Omicron BA.1 variant virus, assessed at Day 14 following initial study vaccination.

Endpoints for 6th Secondary Objective

- MN_{50} GMTs to the ancestral (Wuhan) and Omicron BA.1 viruses at relevant time points (Days 0, 7, 14, 28, 240) and analyzed by previous vaccine combination received. Derived/calculated endpoints based on these data will include GMFR and SRRs.

Endpoints for 7th Secondary Objective

- IgG GMCs to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 S proteins at relevant time points (Days 0, 7, 14, 28, 240) and analyzed by previous vaccine combination received. Derived/calculated endpoints based on these data will include GMFR and SRRs.

Endpoints for 8th Secondary Objective

- GMTs to the ancestral (Wuhan), Omicron BA.1, and Omicron BA.5 S proteins at relevant time points (Days 0, 7, 14, 28, and 240) and analyzed by previous vaccine combination received. Derived/calculated endpoints based on these data will include GMFR and SRRs.

Endpoints for 9th Secondary Objective

- Incidence, duration, and severity of solicited local and systemic adverse events (AEs) for 7 days following vaccination.

- Incidence, severity, and relationship of unsolicited AEs through 28 days after vaccination.

- Incidence and relationship of medically attended adverse events (MAAEs), adverse events of special interest (AESIs) (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and serious adverse events (SAEs) throughout the study.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

The applicant specified the following analysis populations:

- All Randomized Participants Analysis Set: all participants who were randomized, regardless of whether they actually received any study vaccine.
- Full Analysis Set: all participants who were randomized and received at least 1 dose of study vaccine, regardless of protocol violations or missing data, and would be analyzed according to the treatment as randomized.
- Safety Analysis Set: all participants who provided consent, were randomized, and received at least 1 dose of study vaccine. Participants in the Safety Analysis Set would be analyzed as actually treated.
- Per-Protocol Analysis Sets (PP and PP-2): the Per-Protocol (PP) Analysis Set would be determined for each strain, serology assay and study visit. The PP Analysis set would include all participants who received the full prescribed regimen of the study vaccine up to the visit according to protocol, had serology or Intracellular cytokine staining/ Peripheral blood mononuclear cell (ICCS/PBMC) results for baseline and the time point analyzed, were negative at baseline for SARS-CoV-2 (both anti-N and PCR), and had no major protocol violations or an event (e.g., COVID-19 infection) that were considered clinically relevant to impact immunogenicity response as determined prior to database lock. An additional per-protocol analysis set (PP-2) would be defined exactly as the PP analysis set except that it did not require negative baseline anti-N. Within the PP Analysis Set there were 4 subsets defined (for each of the assays used).

Analysis of Immunogenicity

The GMTRs at Day 14 and the two-sided 95% CIs were to be estimated using an analysis of covariance with the vaccine group as a fixed effect and the titer at baseline (pre-vaccination) as a covariate. Titers below the LLOQ were imputed by 0.5 × LLOQ for GMT calculations. The exact 2-sided 95% CIs for percentage of participants with seroresponse were based on the F distribution (Clopper-Pearson). The difference in SRRs and the 95% CI for the difference were to be based on the method of Miettinen and Nurminen. The primary immunogenicity analysis was planned to be performed using the PP Analysis Set. Additional analyses were also planned to be performed using the PP-2 Analysis Set that did not exclude those participants who had a positive anti-N result at baseline.

Analysis of Safety

There was no hypothesis testing specified for the safety objective. The safety analyses were conducted in the Safety Analysis Set. Participants were to be summarized by vaccine group according to the study intervention they actually received. The proportion of participants reporting each event was summarized and the respective 95% CI was based on the Clopper-Pearson method.

Missing Data

Missing baseline PCR results will be imputed as negative ("not detected"). Missing baseline anti-N results will not be imputed. No imputations will be made for missing PCR results from nasal swabs collected at unscheduled visits.

Interim Analysis

A formal analysis was to be carried out when the complete data are available to evaluate the primary endpoints. A set of secondary endpoints were also to be analyzed at this time, dependent on the availability of data. The database extract date was expected to include MN_{50} neutralizing antibody data for Day 14 and safety data through Day 14. The primary statistical hypotheses were to be tested with full Type I error of 5% (two-sided), in the sequential manner.

Multiplicity Adjustment

Adjustments for multiplicity (i.e. control of overall study Type 1 error) were handled by hierarchical testing of statistical hypotheses. All the testing was to be performed based on the immunogenicity data at Day 14 post vaccination.

The co-primary endpoints were evaluated first by testing two hypotheses to compare NVX-CoV2515 (Group C) and NVX-CoV2373 (Group D). Specifically,

1. The first hypothesis tested was

H_0: GMTR ($GMT_{NVX2515}/GMT_{NVX2373}$) ≤ 1.0 vs.
H_1: GMTR ($GMT_{NVX2515}/GMT_{NVX2373}$) > 1.0.

Here, GMTR was defined as the ratio of GMT of the NVX2515 group and the GMT of the NVX2373 group. This null hypothesis would be rejected if the LB of the two-sided 95% CI of the GMTR was above 1.

2. The second hypothesis tested was

H_0: $SRR_{NVX2515}$-$SRR_{NVX2373} \leq -5\%$ vs.
H_1: $SRR_{NVX2515}$-$SRR_{NVX2373} > -5\%$

Here, $SRR_{NVX2515}$ and $SRR_{NVX2373}$ denotes the seroresponse rates in NVX2515 and NVX2373 groups, respectively. The null hypothesis would be rejected if the LB of the two-sided 95% CI of the difference of SRRs was greater than -5%.
For the primary objective, both hypotheses needed to be rejected.

If the primary objective was met, the comparison of the Bivalent vaccine (Group E) to NVX-CoV2515 (Group C) and NVX-CoV2373 (Group D) were to be performed hierarchically following the sequence outlined below:

1. Noninferiority of Group E versus Group C in terms of GMTR against BA.1 pseudovirus MN titer (success criterion: LB of 95% CI of GMTR>0.67).
2. If the noninferiority of Group E to Group C was established, the following three hypotheses would be tested simultaneously:
    a. Superiority of Group E compared to Group D based on the GMTR (success criterion: LB of 95% CI of GMTR>1).
    b. Noninferiority of Group E compared to Group D for ancestral Wuhan strain based on GMTR (success criterion: LB of 95% CI of GMTR>0.67).
    c. Noninferiority of Group E compared to Group D for ancestral Wuhan strain based on SRR (success criterion: LB of 95% CI difference of SRR> -5%).

Sample Size

For the GMTR analysis, assuming a standard deviation of 0.6 for log10-transformed neutralization titers based on data from previous studies, a 15% non-evaluable rate, and an overall one-sided Type I error of 2.5%, Table 2 presents the sample sizes required to achieve 95% power to demonstrate superiority given various assumed true between-group ratios (GMTR) of antibodies to Omicron BA.1 subvariant.

Table 2: Sample Size Calculations

True between-group ratio (NVX-CoV2515 / NVX-CoV2373)	NVX-CoV2515	NVX-CoV2373	Total
1.1	6424	6424	12848
1.2	1757	1757	3514
1.3	851	851	1702
1.4	518	518	1036
1.5	357	357	714
1.6	266	266	532
1.7	210	210	420
1.8	171	171	342
1.9	144	144	288
2.0	124	124	248

Source: Table 8 of the clinical study report (CSR) of Study 311 Part 1 submitted to BLA 125817/0.4.

The sample size Groups C and D (N=360 each) reflected an assumed between-group ratio of 1.5 for NVX-CoV2515 relative to NVX-CoV2373.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The study enrolment was halted before reaching the planned population of 1340 participants after re-examination of the sample size indicated that the necessary number of participants were already enrolled to assess the primary endpoints. As a result, a total of 953 healthy adults (male and nonpregnant females) aged ≥ 18 and ≤ 64 years of age were enrolled in 18 centers in Australia.

6.1.10.1.1 Demographics

The demographic characteristics of the Safety Analysis Set are shown in Table 3. All subjects in the study were from Australia. Demographic and baseline characteristics of the participants in the Safety Analysis Set were generally balanced between the vaccine groups. The median age of all the subjects in the safety analysis set was 41 years. The majority of participants were White (80.1%). The median age of the participants in Groups

A (31 years) and B (38 years) were generally lower than Groups C (42 years), D (41 years) and E (41 years). This was expected since the initial COVID-19 vaccines were approved for older individuals and were later extended to lower age groups. The demographic characteristics in the PP Day 14 Analysis Set were generally similar to the Safety Analysis Set except for a lower proportion of obese participants in Group E (23.8%) compared to other four groups (31.2% to 36.2%). The demographic characteristics in the and PP-2 analysis set were similar to Safety Analysis Set.

Table 3: Participant Demographics and Baseline Disease Characteristics (Safety Analysis Set)

Characteristic	**2 Prior Doses Group A NVX-COV2515 N=61**	**2 Prior Doses Group B NVX-COV2373 N=61**	**3 Prior Doses Group C NVX-COV2515 N=286**	**3 Prior Doses Group D NVX-COV2373 N=274**	**3 Prior Doses Group E NVX-CoV2373+ NVX-CoV2515 N=269**	**Total N=951**
Age (years)						
Mean (SD)	34.1 (12.50)	36.1 (13.49)	40.4 (12.14)	40.1 (11.51)	39.9 (12.35)	39.5 (12.24)
Median	31.0	38.0	42.0	41.0	41.0	41.0
Min – max	18 – 63	18 – 64	18 – 64	18 – 64	18 – 64	18 – 64
Sex, n (%)						
Male	22 (36.1)	22 (36.1)	133 (46.5)	131 (47.8)	118 (43.9)	426 (44.8)
Female	39 (63.9)	39 (63.9)	153 (53.5)	143 (52.2)	151 (56.1)	525 (55.2)
Race, n (%)	--	--	--	--	--	--
White	47 (77.0)	47 (77.0)	233 (81.5)	215 (78.5)	220 (81.8)	762 (80.1)
Black or African American	1 (1.6)	0	0	2 (0.7)	0	3 (0.3)
Aboriginal Australian	0	3 (4.9)	2 (0.7)	1 (0.4)	2 (0.7)	8 (0.8)
Native Hawaiian or other Pacific Islander	2 (3.3)	0	1 (0.3)	0	1 (0.4)	4 (0.4)
Asian	11 (18.0)	9 (14.8)	37 (12.9)	45 (16.4)	39 (14.5)	141 (14.8)
Mixed Origin	0	0	5 (1.7)	3 (1.1)	1 (0.4)	9 (0.9)
Other	0	2 (3.3)	8 (2.8)	8 (2.9)	6 (2.2)	24 (2.5)
Not Reported	0	0	0	0	0	0
Ethnicity, n (%)						
Australian	50 (82.0)	54 (88.5)	252 (88.1)	236 (86.1)	233 (86.6)	825 (86.8)
Aboriginal/Torres Strait Islanders	1 (1.6)	2 (3.3)	4 (1.4)	3 (1.1)	2 (0.7)	12 (1.3)
Hispanic or Latino	2 (3.3)	1 (1.6)	6 (2.1)	8 (2.9)	6 (2.2)	23 (2.4)
Not reported	6 (9.8)	0	12 (4.2)	15 (5.5)	17 (6.3)	50 (5.3)
Unknown	2 (3.3)	3 (4.9)	10 (3.5)	11 (4.0)	9 (3.3)	35 (3.7)
Missing	0	1 (1.6)	2 (0.7)	1 (0.4)	2 (0.7)	6 (0.6)
BMI (kg/m^2)						
n	61	61	284	270	267	943
Mean (SD)	26.97 (10.849)	27.61 (6.261)	28.07 (6.436)	28.01 (5.321)	27.40 (5.686)	27.76 (6.307)
Median	25.40	26.00	26.90	27.50	26.30	26.60
Min – max	16.3 – 99.2	18.6 – 47.2	18.1 – 55.8	17.4 – 47.2	17.7 – 50.1	16.3 – 99.2

Characteristic	2 Prior Doses Group A NVX-COV2515 N=61	2 Prior Doses Group B NVX-COV2373 N=61	3 Prior Doses Group C NVX-COV2515 N=286	3 Prior Doses Group D NVX-COV2373 N=274	3 Prior Doses Group E NVX-CoV2373+ NVX-CoV2515 N=269	Total N=951
BMI (kg/m^2) category, n (%)						
Underweight (<18.0)	1 (1.6)	0	0	3 (1.1)	2 (0.7)	6 (0.6)
Normal (18.0 – 24.9)	27 (44.3)	27 (44.3)	106 (37.1)	75 (27.4)	104 (38.7)	339 (35.6)
Overweight (25.0 – 29.9)	17 (27.9)	17 (27.9)	87 (30.4)	108 (39.4)	90 (33.5)	319 (33.5)
Obese (≥30.0)	16 (26.2)	17 (27.9)	91 (31.8)	84 (30.7)	71 (26.4)	279 (29.3)
Missing	0	0	2 (0.7)	4 (1.5)	2 (0.7)	8 (0.8)
Regimen of previous COVID-19 vaccine, n (%)						
Moderna	3 (4.9)	6 (9.8)	0	2 (0.7)	5 (1.9)	16 (1.7)
Pfizer-BioNTech	58 (95.1)	55 (90.2)	213 (74.5)	214 (78.1)	200 (74.3)	740 (77.8)
Mixed	0	0	73 (25.5)	58 (21.2)	64 (23.8)	195 (20.5)
Moderna-Moderna-Pfizer	0	0	1 (0.3)	1 (0.4)	0	2 (0.2)
Moderna-Pfizer-Pfizer	0	0	2 (0.7)	0	1 (0.4)	3 (0.3)
Moderna-Pfizer-Moderna	0	0	0	0	0	0
Pfizer-Pfizer-Moderna	0	0	70 (24.5)	56 (20.4)	63 (23.4)	189 (19.9)
Pfizer-Moderna-Moderna	0	0	0	1 (0.4)	0	1 (0.1)
Pfizer-Moderna-Pfizer	0	0	0	0	0	0
Previous COVID-19, n (%)						
Yes	4 (6.6)	3 (4.9)	18 (6.3)	22 (8.0)	17 (6.3)	64 (6.7)
No	57 (93.4)	58 (95.1)	268 (93.7)	252 (92.0)	252 (93.7)	887 (93.3)
Qualitative anti-N, n (%)						
Positive	42 (68.9)	44 (72.1)	145 (50.7)	141 (51.5)	134 (49.8)	506 (53.2)
Negative	19 (31.1)	17 (27.9)	141 (49.3)	133 (48.5)	135 (50.2)	445 (46.8)
PCR, n (%)						
Positive	2 (3.3)	1 (1.6)	11 (3.8)	12 (4.4)	14 (5.2)	40 (4.2)
Negative	59 (96.7)	60 (98.4)	275 (96.2)	262 (95.6)	255 (94.8)	911 (95.8)
Anti-N / PCR, n (%)[a]						
Positive	43 (70.5)	44 (72.1)	149 (52.1)	145 (52.9)	137 (50.9)	518 (54.5)
Negative	18 (29.5)	17 (27.9)	137 (47.9)	129 (47.1)	132 (49.1)	433 (45.5)
Time between last previous COVID-19 vaccine and booster dose of study vaccine (days)						
Mean (SD)	278.8 (63.21)	268.6 (51.18)	178.2 (38.49)	182.3 (36.36)	178.7 (36.57)	191.8 (51.13)
Median	268.0	266.0	177.0	182.0	180.0	185.0
Minimum – maximum	137 – 463	135 – 456	84 – 440	91 – 329	77 – 313	77 – 463

Characteristic	2 Prior Doses Group A NVX-COV2515 N=61	2 Prior Doses Group B NVX-COV2373 N=61	3 Prior Doses Group C NVX-COV2515 N=286	3 Prior Doses Group D NVX-COV2373 N=274	3 Prior Doses Group E NVX-CoV2373+ NVX-CoV2515 N=269	Total N=951
Interval between last previous COVID-19 vaccine and booster dose of study vaccine, n (%)						
<90 days	0	0	1 (0.3)	0	1 (0.4)	2 (0.2)
90 – 120 days	0	0	15 (5.2)	15 (5.5)	18 (6.7)	48 (5.0)
>120 – 150 days	1 (1.6)	1 (1.6)	43 (15.0)	35 (12.8)	36 (13.4)	116 (12.2)
>150 – 180 days	0	0	98 (34.3)	81 (29.6)	81 (30.1)	260 (27.3)
>180 – 210 days	4 (6.6)	4 (6.6)	87 (30.4)	97 (35.4)	94 (34.9)	286 (30.1)
>210 – 240 days	7 (11.5)	13 (21.3)	26 (9.1)	32 (11.7)	25 (9.3)	103 (10.8)
>240 – 270 days	22 (36.1)	16 (26.2)	10 (3.5)	9 (3.3)	11 (4.1)	68 (7.2)
>270 – 300 days	15 (24.6)	14 (23.0)	4 (1.4)	2 (0.7)	1 (0.4)	36 (3.8)
>300 – 330 days	5 (8.2)	9 (14.8)	1 (0.3)	3 (1.1)	2 (0.7)	20 (2.1)
>330 – 360 days	1 (1.6)	1 (1.6)	0	0	0	2 (0.2)
>360 days	6 (9.8)	3 (4.9)	1 (0.3)	0	0	10 (1.1)

Abbreviations: anti-N=anti-nucleocapsid; BMI=body mass index; COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction; SD=standard deviation.
Note: Age was calculated at the time of informed consent.
Note: n for continuous parameters represents the number of participants with non-missing values for that parameter.
Note: BMI was calculated as weight (kg) divided by squared height (m). Percentages were based on the Safety Analysis Set within each treatment and overall.
a. Participants with either anti-N or PCR are reported.
Source: Adapted from Table 16 of Final CSR for Study 311 Part 1 submitted to BLA 125817/0.4.

6.1.10.1.3 Subject Disposition

The subject disposition information for Study 311 Part 1 is summarized in Table 4. The number of subjects included in the PP Analysis Set 2 was similar to that in the Safety Analysis Set. PP Analysis Set at Day 14 included a substantially lower number of subjects compared to the PP Analysis Set 2 since a large proportion of subjects were excluded due to positive anti-N result at baseline. The proportions of subjects excluded from any specific reason were similar across all five treatment arms.

Table 4: Subjects Disposition and Analysis Sets (All Randomized Participants)

	2 Prior Doses Group A NVX-CoV2515 n (%)	2 Prior Doses Group B NVX-CoV2373 n (%)	3 Prior Doses Group C NVX-CoV2515 n (%)	3 Prior Doses Group D NVX-CoV2373 n (%)	3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 n (%)
All Randomized Participants Analysis Set	61 (100)	61 (100)	279 (100)	274 (100)	278 (100)
Full-Analysis Set	61 (100)	61 (100)	279 (100)	273 (99.6)	277 (99.6)

	2 Prior Doses Group A NVX-CoV2515 n (%)	2 Prior Doses Group B NVX-CoV2373 n (%)	3 Prior Doses Group C NVX-CoV2515 n (%)	3 Prior Doses Group D NVX-CoV2373 n (%)	3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 n (%)
Safety Analysis Set [1]	61 (100)	61 (100)	286 (102.5)	274 (100)	269 (96.8)
Per-Protocol Analysis Set					
Day 14					
Included	15 (24.6)	14 (23.0)	124 (44.4)	116 (42.3)	116 (41.7)
Excluded	46 (75.4)	47 (77.0)	155 (55.6)	157 (57.3)	161 (57.9)
Baseline Positive PCR result	2 (3.3)	1 (1.6)	11 (3.9)	12 (4.4)	14 (5.0)
Baseline Positive Anti-N result	42 (68.9)	44 (72.1)	141 (50.5)	141 (51.5)	138 (49.6)
Baseline Missing Anti-N Result	0	0	0	0	0
Sample not collected (Baseline or the Visit Analyzed)	5 (8.2)	1 (1.6)	5 (1.8)	7 (2.6)	8 (2.9)
COVID-19 Infection Prior to Visit	2 (3.3)	3 (4.9)	7 (2.5)	4 (1.5)	9 (3.2)
Protocol Deviation	3 (4.9)	3 (4.9)	10 (3.6)	13 (4.7)	17 (6.1)
Day 28					
Included	12 (19.7)	12 (19.7)	116 (41.6)	111 (40.5)	108 (38.8)
Excluded	49 (80.3)	49 (80.3)	163 (58.4)	162 (59.1)	169 (60.8)
Baseline Positive PCR result	2 (3.3)	1 (1.6)	11 (3.9)	12 (4.4)	14 (5.0)
Baseline Positive Anti-N result	42 (68.9)	44 (72.1)	141 (50.5)	141 (51.5)	138 (49.6)
Baseline Missing Anti-N Result	0	0	0	0	0
Sample not collected (Baseline or the Visit Analyzed)	3 (4.9)	1 (1.6)	5 (1.8)	4 (1.5)	6 (2.2)
COVID-19 Infection Prior to Visit	6 (9.8)	4 (6.6)	11 (3.9)	11 (4.0)	20 (7.2)
Protocol Deviation	2 (3.3)	4 (6.6)	15 (5.4)	16 (5.8)	25 (9.0)
Per-Protocol Analysis Set 2					
Day 14					
Included	51 (83.6)	55 (90.2)	250 (89.6)	245 (89.4)	235 (84.5)
Excluded	10 (16.4)	6 (9.8)	29 (10.4)	28 (10.2)	42 (15.1)
Baseline positive PCR result	2 (3.3)	1 (1.6)	11 (3.9)	12 (4.4)	14 (5.0)
Sample not collected (Baseline or the Visit Analyzed)	5 (8.2)	1 (1.6)	5 (1.8)	7 (2.6)	8 (2.9)
COVID-19 Infection Prior to Visit	2 (3.3)	3 (4.9)	7 (2.5)	4 (1.5)	9 (3.2)
Protocol Deviation	3 (4.9)	3 (4.9)	10 (3.6)	13 (4.7)	17 (6.1)
Day 28					
Included	49 (80.3)	51 (83.6)	241 (86.4)	236 (86.1)	221 (79.5)

	2 Prior Doses Group A NVX-CoV2515 n (%)	2 Prior Doses Group B NVX-CoV2373 n (%)	3 Prior Doses Group C NVX-CoV2515 n (%)	3 Prior Doses Group D NVX-CoV2373 n (%)	3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 n (%)
Excluded	12 (19.7)	10 (16.4)	38 (13.6)	37 (13.5)	56 (20.1)
Baseline positive PCR result	2 (3.3)	1 (1.6)	11 (3.9)	12 (4.4)	14 (5.0)
Sample not collected (baseline or the Visit analyzed)	3 (4.9)	1 (1.6)	5 (1.8)	4 (1.5)	6 (2.2)
COVID-19 infection prior to visit	6 (9.8)	4 (6.6)	11 (3.9)	11 (4.0)	20 (7.2)
Protocol deviation	2 (3.3)	4 (6.6)	15 (5.4)	16 (5.8)	25 (9.0)

[1] Eight participants assigned to the bivalent vaccine group (Group E) did not receive the vaccine randomly assigned to them: 7 participants received NVX-CoV2515 (Group C), and 1 participant received NVX-CoV2373 (Group D).
Source: Table 14 of the clinical study report (CSR) of Study 311 Part 1 submitted to BLA 125817/0.4.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The results of the primary immunogenicity analysis in the PP Analysis Sets are shown in Table 5. Success criteria were met for both co-primary endpoints. Namely, at Day 14, the GMTR of NVX-CoV2515 versus NVX-CoV2373 against the Omicron BA.1 subvariant was 1.6, 95% CI (1.33, 2.03), with a lower bound of 1.33 (>1) in the PP Day 14 Neutralization Assay Analysis Set. The respective difference in SRRs between NVX-CoV2515 and NVX-CoV2373 was 22.5%, 95% CI (10.3%, 34.2%), with a lower bound of 10.3% (>-5%) in the PP Day 14 Neutralization Assay Analysis Set. The results in the PP-2 Day 14 Neutralization Assay Analysis Set are shown in Table 6 and showed a GMTR of 1.5, 95% CI (1.34, 1.76) for NVX-CoV2515 versus NVX-CoV2373 against the Omicron BA.1 subvariant and a difference in SRRs of 22.3%, 95% CI (13.6%, 30.6%) between NVX-CoV2515 and NVX-CoV2373. Similarly, in the PP-2 Day 28 Neutralization Assay Analysis Set the GMTR of NVX-CoV2515 versus NVX-CoV2373 against the Omicron BA.1 subvariant was 1.5, 95% CI (1.28, 1.72) and the difference in SRRs between NVX-CoV2515 and NVX-CoV2373 was 24.6%, 95% CI (15.9%, 32.9%). The immunogenicity results in Groups A and B were similar to Groups C and D in PP Day 14 analysis set, respectively, with the caveat that the numbers of subjects are small in Groups A and B (N=15 and N=14, respectively).

Table 5: Serum Neutralizing Antibody Titers Against the Omicron BA.1 Subvariant Virus at Days 0, 14, and 28 after Study Vaccination (PP Neutralization Assay Analysis Set)

Characteristics	**3 Prior Doses Group C NVX-CoV2515 N=126**	**3 Prior Doses Group D NVX-CoV2373 N=119**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=118**
Baseline			
n[a]	126	119	118
Median	20	20	20
Min - Max	10 - 320	10 - 1280	10 - 640
GMT	25.2	27.9	26.7
95% CI	21.5, 29.5	22.9, 33.9	22.3, 31.8
Day 14			
n[a]	124	116	116
Median	160	80	80
Min - Max	10 - 1280	10 - 1280	10 - 1280
GMT	130.8	83.9	95.1
95% CI	109.2, 156.7	69.6, 101.2	79.0, 114.5
GMFR Between Visit and Baseline			
n[b]	124	116	116
Reference to Day 0	5.2	3	3.6
95% CI	4.4, 6.1	2.6, 3.6	3.1, 4.3
SRR (≥ 4-fold increase from Baseline)			
n[c]	91	59	75
Percentage (%)	73.4	50.9	64.7
95% CI (%)	64.7, 80.9	41.4, 60.3	55.2, 73.3
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	1.6	1.2	0.7
95% CI	1.33, 2.03	0.95, 1.45	0.57, 0.88
Difference in SRR (%)	22.5	13.8	-8.7
95% CI (%)	10.3, 34.2	1.1, 26.1	-20.3, 3.0
Day 28			
n[a]	116	110	108
Median	160	80	80
Min - Max	10-2560	10-2560	10-2560
GMT	122.3	77.5	85.9
95% CI	101.0, 148.0	63.1, 95.3	71.2, 103.6
GMFR Between Visit and Baseline			
n[b]	116	110	108
Reference to Day 0	4.8	2.9	3.2
95% CI	4.1, 5.7	2.4, 3.6	2.7, 3.7
SRR (≥ 4-fold increase from Baseline)			
n[c]	86	52	58

Characteristics	**3 Prior Doses Group C NVX-CoV2515 N=126**	**3 Prior Doses Group D NVX-CoV2373 N=119**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=118**
Percentage (%)	74.1	47.3	53.7
95% CI (%)	65.2, 81.8	37.7, 57.0	43.8, 63.3
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	1.6	1.1	0.7
95% CI	1.29, 2.06	0.88, 1.38	0.54, 0.83
Difference in SRR (%)	26.9	6.4	-20.4
95% CI (%)	14.3, 38.7	-6.8, 19.5	-32.5, -7.9

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and Day 28 titers available.

[c]Number of subjects achieving seroresponse from baseline.

Source: Table 14.2.1.1.1.s of the eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR submitted to BLA 125817/0.64.

Table 6: Serum Neutralizing Antibody Titers Against the Omicron BA.1 Subvariant Virus at Days 0, 14, and 28 after Study Vaccination (PP-2 Neutralization Assay Analysis Set)

Characteristics	**3 Prior Doses Group C NVX-CoV2515 N=258**	**3 Prior Doses Group D NVX-CoV2373 N=251**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=240**
Baseline			
n[a]	258	251	240
Median	160	160	160
Min - Max	10-2560	10-2560	10 - 10240
GMT	98.1	106	105
95% CI	80.4, 119.7	86.6, 129.8	85.1, 129.5
Day 14			
n[a]	250	245	235
Median	320	320	320
Min - Max	10-5120	10-2560	10-5120
GMT	316.5	217.8	246.1
95% CI	268.2, 373.4	185.9, 255.2	207.3, 292.2
GMFR Between Visit and Baseline			
n[b]	250	245	235
Reference to Day 0	3.3	2.1	2.4
95% CI	2.9, 3.7	1.8, 2.3	2.1, 2.7
SRR (≥ 4-fold increase from Baseline)			

Characteristics	**3 Prior Doses Group C NVX-CoV2515 N=258**	**3 Prior Doses Group D NVX-CoV2373 N=251**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=240**
n[c]	135	78	96
Percentage (%)	54	31.8	40.9
95% CI (%)	47.6, 60.3	26.1, 38.1	34.5, 47.4
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	1.5	1.1	0.7
95% CI	1.34, 1.76	1.00, 1.30	0.65, 0.85
Difference in SRR (%)	22.2	9	-13.1
95% CI (%)	13.5, 30.5	0.4, 17.5	-21.8, -4.3
Day 28			
n[a]	241	235	221
Median	320	160	160
Min - Max	10-5120	10-2560	10 - 10240
GMT	283.6	195.5	211.5
95% CI	240.7, 334.1	165.6, 230.8	177.4, 252.2
GMFR Between Visit and Baseline			
n[b]	241	235	221
Reference to Day 0	2.8	1.9	2
95% CI	2.5, 3.2	1.6, 2.1	1.8, 2.2
SRR (≥ 4-fold increase from Baseline)			
n[c]	126	65	74
Percentage (%)	52.3	27.7	33.5
95% CI (%)	45.8, 58.7	22.0, 33.9	27.3, 40.1
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	1.5	1.1	0.7
95% CI	1.28, 1.72	0.93, 1.24	0.63, 0.83
Difference in SRR (%)	24.6	5.8	-18.8
95% CI (%)	15.9, 32.9	-2.6, 14.3	-27.5, -9.8

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and Day 28 titers available.

[c]Number of subjects achieving seroresponse from baseline.

Source: Table 14.2.1.1.3.s of the eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR submitted to BLA 125817/0.64.

6.1.11.2 Analyses of Secondary Endpoints

As success criteria for the primary objective were met, hypothesis testing for non-inferiority of immune response induced by the bivalent NVX-CoV2373 + NVX-CoV2515 versus NVX-CoV2515 against Omicron BA.1 subvariant at Day 14 was conducted. The GMTR of NVX-CoV2373 + NVX-CoV2515 versus NVX-CoV2515 against the Omicron BA.1 subvariant was 0.7, 95% CI (0.57, 0.88), with a lower bound of 0.57 (<0.67) in the PP Day 14 Neutralization Assay Analysis Set, failing to meet the pre-specified criterion for this endpoint. Thus, the hierarchical hypothesis testing procedure stopped and the subsequent analyses were considered descriptive. In the PP-2 Day 14 Neutralization Assay Analysis Set, the respective GMTR was 0.7, 95% CI (0.63, 0.83), with a lower bound of 0.63, which is similar to the result in the PP Day 14 Neutralization Assay Analysis Set.

The GMTR of NVX-CoV2373 + NVX-CoV2515 versus NVX-CoV2373 against the Omicron BA.1 subvariant was 1.1, 95% CI (0.93, 1.24), in the PP-2 Day 14 Neutralization Assay Analysis Set.

The immunogenicity results on the serum neutralizing antibody titers against the ancestral (Wuhan) strain virus at Days 0, 14, and 28 after study vaccination in the PP-2 Neutralization Assay Analysis Set are shown in Table 7. Accordingly, the GMTR of NVX-CoV2373 + NVX-CoV2515 versus NVX-CoV2373 against ancestral Wuhan strain was 1.0, 95% CI (0.85, 1.09), in the PP-2 Day 14 Neutralization Assay Analysis Set.

The difference in SRRs between NVX-CoV2373 + NVX-CoV2515 and NVX-CoV2373 against the Omicron BA.1 subvariant was 9%, 95% CI (0.4%, 17.5%), in the PP-2 Day 14 Neutralization Assay Analysis Set (Table 6). The respective result in the PP Day 14 Neutralization Assay Analysis Set was 13.8%, 95% CI (1.1%, 26.1%) (Table 5).

Table 7: Serum Neutralizing Antibody Titers Against the Ancestral (Wuhan) Strain Virus at Days 0, 14, and 28 after Study Vaccination (PP-2 Neutralization Assay Analysis Set)

Characteristics	3 Prior Doses Group C NVX-CoV2515 N=258	3 Prior Doses Group D NVX-CoV2373 N=251	3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=240
Baseline			
n[a]	258	251	240
Median	1280	1280	1280
Min - Max	20 - 40960	20 - 40960	40 - 81920
GMT	1152.7	1272.9	1222.2
95% CI	976.5, 1360.6	1072.6, 1510.8	1019.4, 1465.4
Day 14			
n[a]	250	245	235
Median	2560	2560	2560
Min - Max	80 - 40960	160 - 81920	80 - 163840
GMT	2185.8	2686.1	2507.7
95% CI	1893.9, 2522.6	2334.4, 3090.9	2164.0, 2906.0

Characteristics	3 Prior Doses Group C NVX-CoV2515 N=258	3 Prior Doses Group D NVX-CoV2373 N=251	3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=240
GMFR Between Visit and Baseline			
n[b]	250	245	235
Reference to Day 0	1.9	2.1	2.1
95% CI	1.7, 2.1	1.9, 2.4	1.9, 2.3
SRR (≥ 4-fold increase from Baseline)			
n[c]	79	80	84
Percentage	31.6	32.7	35.7
95% CI	25.9, 37.8	26.8, 38.9	29.6, 42.2
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	0.9	1	1.1
95% CI	0.77, 0.99	0.85, 1.09	0.98, 1.25
Difference in SRR	-1.1	3.1	4.1
95% CI	-9.3, 7.2	-5.4, 11.6	-4.3, 12.5
Day 28			
n[a]	241	235	221
Median	2560	2560	2560
Min - Max	40 - 20480	80 - 40960	160 - 81920
GMT	1909.1	2442	2101
95% CI	1651.0, 2207.6	2133.2, 2795.5	1807.7, 2441.9
GMFR Between Visit and Baseline			
n[b]	241	235	221
Reference to Day 0	1.6	1.9	1.7
95% CI	1.4, 1.8	1.7, 2.2	1.5, 1.9
SRR (≥ 4-fold increase from Baseline)			
n[c]	56	68	60
Percentage	23.2	28.9	27.1
95% CI	18.1, 29.1	23.2, 35.2	21.4, 33.5
Comparison Between Groups	**NVX-CoV2515 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2515) vs NVX-CoV2515**
GMTR	0.8	0.9	1.1
95% CI	0.72, 0.93	0.77, 0.99	0.94, 1.22
Difference in SRR	-5.7	-1.8	3.9
95% CI	-13.6, 2.2	-10.0, 6.5	-4.0, 11.9

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and Day 28 titers available.

[c]Number of subjects achieving seroresponse from baseline.
Source: Table 14.2.1.2.3.s of the eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR submitted to BLA 125817/0.64.

6.1.12 Safety Analyses

6.1.12.1 Solicited Local Adverse Events

A summary of the solicited local adverse events for the five treatment groups is provided in Table 8.

The most frequently reported local reaction after study vaccination was pain/tenderness at the injection site in 78.3%, 72.4%, 69.3%, 70.6%, and 64.6% the subjects in Groups A, B, C, D, and E, respectively. In general, local reactions were reported at similar frequencies between the study groups, regardless of the number of Moderna and/or Pfizer-BioNTech prototype vaccines previously received. Most local reactions were mild to moderate in severity, with very few subjects reporting Grade 3 reactions.

Table 8: Local reactions by maximum severity within 7 days after study vaccination (Safety Analysis Set)

Local Reactions	**2 Prior Doses Group A NVX-CoV2515 N=60 n (%)**	**2 Prior Doses Group B NVX-CoV2373 N=58 n (%)**	**3 Prior Doses Group C NVX-CoV2515 N=283 n (%)**	**3 Prior Doses Group D NVX-CoV2373 N=272 n (%)**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=268 n (%)**
Any local AE					
Any Grade	47 (78.3)	42 (72.4)	196 (69.3)	193 (71.0)	173 (64.6)
Grade 3	1 (1.7)	1 (1.7)	5 (1.8)	1 (0.4)	3 (1.1)
Pain/tenderness					
Any Grade	47 (78.3)	42 (72.4)	196 (69.3)	192 (70.6)	173 (64.6)
Grade 3	1 (1.7)	1 (1.7)	5 (1.8)	1 (0.4)	2 (0.7)
Pain					
Any Grade	33 (55.0)	25 (43.1)	110 (38.9)	109 (40.1)	96 (35.8)
Grade 3	1 (1.7)	0	2 (0.7)	1 (0.4)	0
Tenderness					
Any Grade	40 (66.7)	41 (70.7)	181 (64.0)	175 (64.3)	162 (60.4)
Grade 3	0	1 (1.7)	3 (1.1)	1 (0.4)	2 (0.7)
Redness					
Any Grade	1 (1.7)	1 (1.7)	7 (2.5)	3 (1.1)	3 (1.1)
Grade 3	0	0	0	0	1 (0.4)
Swelling					
Any Grade	0	0	7 (2.5)	3 (1.1)	4 (1.5)
Grade 3	0	0	0	0	0

Source: Adapted from Table 14.3.2.1.1 of the Safety Data Summary Tables submitted to BLA 125817/0.4.

6.1.12.2 Solicited Systemic Adverse Events

As shown in Table 9, the most frequently reported systemic reactions after study vaccination were fatigue (in 40.0% [Group A], 39.7% [Group B], 40.6% [Group C], 37.5% [Group D], 41.0% [Group E]) and headache (in 28.3% [Group A], 36.2% [Group B], 37.5% [Group C], 34.9% [Group D], 35.8% [Group E]). In general, the reported systemic reactions were generally at similar frequencies between the study groups. Most systemic reactions were mild to moderate in severity. There was 1 Grade 4 systemic reaction of fever reported in Group C.

Table 9: Solicited Systemic Adverse Events for 7 Days After Booster Vaccination with Monovalent (Previously Received 2 or 3 Vaccinations With COVID-19 mRNA Vaccines), (Safety Analysis Set)

Adverse Event	**2 Prior Doses Group A NVX-CoV2515 N=60 n (%)**	**2 Prior Doses Group B NVX-CoV2373 N=58 n (%)**	**3 Prior Doses Group C NVX-CoV2515 N=283 n (%)**	**3 Prior Doses Group D NVX-CoV2373 N=272 n (%)**	**3 Prior Doses Group E NVX-CoV2515+NVX-CoV2373 N=268 n (%)**
Any systemic AE					
Any Grade	32 (53.3)	34 (58.6)	176 (62.2)	158 (58.1)	166 (61.9)
Grade 3	3 (5.0)	2 (3.4)	20 (7.1)	10 (3.7)	8 (3.0)
Grade 4	0	0	1 (0.4)	0	0
Fever[a]					
Any Grade	0	1 (1.7)	5 (1.8)	2 (0.7)	1 (0.4)
Grade 3[b]	0	0	1 (0.4)	0	0
Grade 4[c]	0	0	1 (0.4)	0	0
Fatigue/malaise					
Any Grade	24 (40.0)	24 (41.4)	127 (44.9)	111 (40.8)	121 (45.1)
Grade 3	1 (1.7)	2 (3.4)	15 (5.3)	8 (2.9)	7 (2.6)
Fatigue					
Any Grade	24 (40.0)	23 (39.7)	115 (40.6)	102 (37.5)	110 (41.0)
Grade 3	1 (1.7)	2 (3.4)	11 (3.9)	5 (1.8)	6 (2.2)
Malaise					
Any Grade	10 (16.7)	13 (22.4)	66 (23.3)	54 (19.9)	51 (19.0)
Grade 3	1 (1.7)	0	9 (3.2)	5 (1.8)	2 (0.7)
Muscle pain					
Any Grade	13 (21.7)	20 (34.5)	71 (25.1)	66 (24.3)	64 (23.9)
Grade 3	0	1 (1.7)	5 (1.8)	0	0
Joint pain					
Any Grade	11 (18.3)	6 (10.3)	27 (9.5)	29 (10.7)	16 (6.0)
Grade 3	0	0	2 (0.7)	0	1 (0.4)
Nausea/vomiting					
Any Grade	8 (13.3)	4 (6.9)	21 (7.4)	19 (7.0)	23 (8.6)
Grade 3	0	0	0	1 (0.4)	0
Headache					
Any Grade	17 (28.3)	21 (36.2)	106 (37.5)	95 (34.9)	96 (35.8)
Grade 3	2 (3.3)	0	1 (0.4)	3 (1.1)	1 (0.4)

[a]Temperature ≥38°C.
[b]39.0-40°C
[c]>40°C

Source: Adapted from Table 14.3.2.1.1 of the Safety Data Summary Tables submitted to BLA 125817/0.4.

6.1.12.2 Unsolicited Adverse Events

A summary of unsolicited adverse events for Groups C, D and E is provided in Table 10. Related MAAEs, Serious TEAEs, PIMMCs, AESIs, Myocarditis/Pericarditis, and TEAEs leading to any discontinuation were reported through end of study. Other TEAEs were reported through 28 days after study vaccination. The proportion of subjects who reported unsolicited TEAEs post vaccination was slightly higher in NVX-CoV2373 group (38.3%) compared to NVX-CoV2515 group (32.2%) or bivalent NVX-CoV2373 + NVX-CoV2515 (33.5%). The proportion of subjects who reported at l least one SAE throughout the study was slightly higher in Group C (2.8%) compared to Groups D (1.5%) and E (1.5%).

For Groups A and B, 18 (29.5%) and 19 (31.1%) of the subjects, respectively, reported unsolicited TEAEs within 28 days postvaccination. The numbers of subjects who reported at least one SAE throughout the study was 1 (1.6%) and 2 (3.3%), respectively, for groups A and B respectively. No AESIs were reported in Groups A and B for the duration of the study.

Table 10: Summary of Unsolicited Adverse Events after Study Vaccination (Safety Analysis Set)

Parameters	**3 Prior Doses Group C NVX-CoV2515 N=286**	**3 Prior Doses Group D NVX-CoV2373 N=274**	**3 Prior Doses Group E NVX-CoV2515+ NVX-CoV2373 N=269**
Any unsolicited TEAE	92 (32.2)	105 (38.3)	90 (33.5)
Treatment-related	13 (4.5)	8 (2.9)	7 (2.6)
Severe	0	4 (1.5)	0
Treatment-related severe	0	0	0
Any unsolicited serious TEAE	8 (2.8)	4 (1.5)	4 (1.5)
Treatment-related	0	0	0
Any unsolicited TEAE leading to study discontinuation	0	1 (0.4)	0
Treatment-related	0	0	0
Any unsolicited treatment-emergent MAAE	14 (4.9)	18 (6.6)	11 (4.1)
Treatment-related	1 (0.3)	0	0
Treatment-related serious MAAE	0	0	0
Severe MAAE	0	3 (1.1)	0
Related Severe MAAE	0	0	0
Any unsolicited AESI: PIMMC[1]	2 (0.7)	2 (0.7)	1 (0.4)
Treatment-related	0	0	0
Any unsolicited AESI: complications due to COVID-19	0	0	0

Parameters	3 Prior Doses Group C NVX-CoV2515 N=286	3 Prior Doses Group D NVX-CoV2373 N=274	3 Prior Doses Group E NVX-CoV2515+ NVX-CoV2373 N=269
Any myocarditis/pericarditis	0	0	0

[1]PIMMCs were recorded according to protocol-defined criteria and by the investigator reporting in the CRF.
Source: Adapted from Table 14.3.1.1 of the Safety Data Summary Tables submitted to BLA 125817/0.4.

6.1.12.3 Deaths

No deaths occurred in the study.

6.2 Study 2019nCoV-311 Part 2

Part 2 of Study 2019nCoV-311 evaluated the immunogenicity and safety of 2 booster doses of NVX-CoV2540 and NVX-CoV2373 alone and bivalent prototype and Omicron BA.5 subvariant vaccine (NVX-CoV2373 + NVX-CoV2540) in previously vaccinated (i.e., ≥ 3 doses of the Moderna and/or Pfizer- BioNTech prototype COVID-19 vaccines) adults ≥ 18 years of age.

6.2.1 Objectives

Primary Objective

1. To determine if bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induces superior antibody responses compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA vaccines.

Secondary Objectives

1. To assess neutralizing antibodies induced by the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) and NVX-CoV2373 to the ancestral (Wuhan) and Omicron BA.5 strains over time in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines.

2. To assess IgG antibody levels induced by the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) and NVX-CoV2373 to the ancestral (Wuhan) and Omicron BA.5 strains and in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines.

3. To assess antibody responses in a hACE2 receptor binding inhibition assay induced by the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) and NVX-CoV2373 to the ancestral (Wuhan) and Omicron BA.5 strains in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines.

4. To assess the overall safety after 1 and 2 doses of bivalent (NVX-CoV2373 + NVX-CoV2540) vaccine and NVX-CoV2373 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines.

5. To assess the overall safety after 1 and 2 doses of NVX-CoV2540 in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines.

6.2.2 Design Overview

Study 2019nCoV-311 Part 2 was a Phase 3, randomized, observer-blinded study evaluating the safety and immunogenicity of 2 booster doses of the Omicron BA.5 subvariant vaccine (NVX-CoV2540) and the prototype Novavax vaccine (NVX-CoV2373) alone and bivalent prototype and Omicron subvariant vaccines (NVX-CoV2373 + NVX-CoV2540) in adults ≥ 18 years of age who previously received ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously.

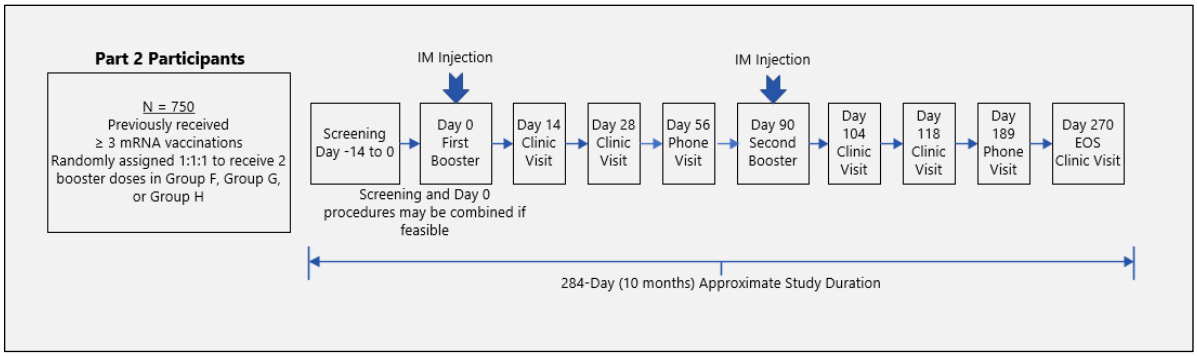
Approximately 750 medically stable adult participants were planned to be randomly assigned in a 1:1:1 ratio to receive 2 booster doses of study vaccine (on Day 0 and Day 90) in Group F, Group G, and Group H as follows:

- Group F: 2 doses of NVX-CoV2540 (on Day 0 and Day 90)
- Group G: 2 doses of NVX-CoV2373 (on Day 0 and Day 90)
- Group H: 2 doses of bivalent NVX-CoV2373 + NVX-CoV2540 (on Day 0 and Day 90)

Randomization was stratified by age group (18 to 54 years; ≥ 55 years). Participants were to remain on study for immunogenicity and safety data collection through Day 270. The study vaccines were administered in blinded manner as intramuscular (IM) injections.

The design of Study 311 Part 2 is described in Figure 2. Part 2 consisted of a screening period (Days -14 to 0); first study vaccination day (Day 0); clinic visits on Days 14, 28, and 90 (second study vaccination day), 104, and 118; and phone calls on Days 56 and 189. The duration of individual participation, including screening, would be a maximum of 10 months (Day 270 ± 15 days) from the first booster vaccination.

Figure 2: Study Design of Study 311 Part 2



Abbreviations: EOS = end of study; IM = intramuscular.
Group F = NVX-CoV2540 Day 0, NVX-CoV2540 Day 90.
Group G = NVX-CoV2373 Day 0, NVX-CoV2373 Day 90.
Group H = Bivalent NVX-CoV2373 + NVX-CoV2540 Day 0, Bivalent NVX-CoV2373 + NVX-CoV2540 Day 90.
Source: Figure 2 of the Protocol of Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.3 Population

Male and nonpregnant female participants ≥ 18 years of age who were medically stable and had previously received ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent vaccines ≥ 90 days prior to study vaccination.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The investigational products were NVX-CoV2373, NVX-CoV2540 and Prototype/BA.5 Bivalent Vaccine (Site-mixed, NVX-CoV2373+NVX-CoV2540). Details of NVX-CoV2373 can be found in the study treatment section of Study 311 Part 1 (Section 6.1.4).

NVX-CoV2540 (5 µg) is a coformulated Omicron BA.5 SARS-CoV-2 rS vaccine with Matrix-M adjuvant: supplied as a solution for preparation for injection, at a concentration of 10 µg antigen and 100 µg adjuvant per mL.

The Bivalent vaccine containing antigens for the prototype SARS-CoV-2 strain and Omicron BA.5 subvariant, was prepared from study supplies of NVX-CoV2373 and NVX-CoV2540. The bivalent vaccine was prepared and drawn into a syringe on the day of administration by a qualified member of study site personnel. All injections were administered in a 0.5 mL injection volume at a dose of 5 µg total antigen (2.5 µg prototype antigen + 2.5 µg Omicron BA.5 antigen) with 50 µg Matrix-M adjuvant.

6.2.6 Sites and Centers

This study was conducted at 21 sites in Australia.

6.2.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

6.2.8 Endpoints and Criteria for Study Success

Co-primary Endpoints:

- Neutralizing antibody (NAb) GMTs to the Omicron BA.5 subvariant, assessed at Day 28 following initial study vaccination.

- SRRs in NAb titer concentrations to the Omicron BA.5 subvariant, assessed at Day 28 following initial study vaccination. SRR was defined as the proportion of participants who had,
    - At least a 4-fold increase from baseline (Day 0) if the baseline value is equal to or above the lower limit of quantification (LLOQ) or
    - At least 4 times the LLOQ if the baseline value is below the LLOQ.

- NAb GMTs to the ancestral (Wuhan) strain, assessed at Day 28 following initial study vaccination.

Secondary Endpoints:

Endpoints corresponding to the 1st Secondary Objective:

- NAb GMTs to the ancestral (Wuhan) and Omicron BA.5 strains at relevant time points (Days 0, 28, 90, 104, and 118) and analyzed by age group (overall, 18 to 54, and ≥ 55 years of age).

- NAb GMFR to the ancestral (Wuhan), and Omicron BA.5 strains at relevant time points (Days 28, 104, and 118) from baseline (Day 0 or Day 90) and analyzed by age group (overall, 18 to 54, and ≥ 55 years of age).

- SRRs in NAb titers to the ancestral (Wuhan) and Omicron BA.5 strains at relevant time points (Days 28, 104, and 118) and analyzed by age group (overall, 18 to 54, and ≥ 55 years of age).

Endpoints corresponding to the 2nd Secondary Objective:

- IgG GMEUs to the ancestral (Wuhan) and Omicron BA.5 S proteins at relevant time points (Days 0, 28, 90, 104, and 118) and analyzed by age group (overall, 18 to 54, and ≥ 55 years of age). Derived/calculated endpoints based on these data included GMFR and SRRs.

Endpoints corresponding to the 3rd Secondary Objective:

- GMTs to the ancestral (Wuhan) and Omicron BA.5 S proteins at relevant time points (Days 0, 28, 90, 104, and 118) and analyzed by age group (overall, 18 to

54, and ≥ 55 years of age). Derived/calculated endpoints based on these data included GMFR and SRRs.

Endpoints corresponding to the 4th Secondary Objective:

- Incidence, duration, and severity of solicited local and systemic AEs for 7 days following each vaccination.

- Incidence, severity, and relationship of unsolicited AEs through 28 days following each vaccination.

- Incidence and relationship of MAAEs, AESIs (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and SAEs throughout the study.

Endpoints corresponding to the 5th Secondary Objective:

- Incidence, duration, and severity of solicited local and systemic AEs for 7 days following each vaccination.

- Incidence, severity, and relationship of unsolicited AEs through 28 days following each vaccination.

- Incidence and relationship of MAAEs, AESIs (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and SAEs throughout the study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

Randomized Participants Analysis Set included all participants who were randomized/enrolled, regardless of whether they actually received any study vaccine. The Randomized Participants Analysis Set was used for participant disposition summaries and was analyzed according to the vaccine group as randomized/enrolled.

The Full Analysis Set (FAS) included all participants who were randomized/enrolled and received at least 1 dose of study vaccine, regardless of protocol violations or missing data. The FAS may be the secondary analysis set used for any immunogenicity analyses should there by high enough exclusion of participants from the per protocol analysis.

The Safety Analysis Set included all participants who provided consent, were randomized, and received at least 1 dose of study vaccine. Participants in the Safety Analysis Set were analyzed according to the vaccine group that was actually administered based on the first dose received. Of note, no subjects received different vaccines for the first and second

doses in this study.

The Per-Protocol (PP) Analysis Set was determined for each strain, serology assay, and study visit. The PP Analysis Set reflected the participants (or subsets thereof) selected to have their blood samples tested for each assay, strain, and time point. The PP Analysis Set included all participants who received the full prescribed regimen of the study vaccine up to the visit according to protocol, had serology or ICCS/PBMC results for baseline and the time point analyzed, were PCR negative at baseline for SARS-CoV-2, and had no major protocol violations (e.g., dosed with material other than the assigned group) or an event (e.g., COVID-19 infection) that was considered clinically relevant to impact immunogenicity response as determined prior to database lock. Within the PP Analysis Set there were 4 subsets, namely, Anti-S Protein Serology PP Analysis Subset (PP-S), Neutralization Assay PP Analysis Subset (PP-N), hACE2 Receptor Binding Inhibition Assay Subset (PP-h) and ICCS/PBMC Analysis Subset (PP-C). These subsets were considered for the strain specific immunogenicity analyses.

Analysis of Immunogenicity

The analysis of the primary immunogenicity endpoints was performed using the PP Analysis Set and the Neutralization Assay Subset in participants in Groups G and H. The co-primary endpoints focused on neutralizing antibodies to Omicron BA.5 and ancestral (Wuhan) strains. GMT was calculated as the antilog of the mean of the log-transformed titers at Day 28. GMFR was calculated as the antilog of the mean of the log-transformed ratio of titers at Day 28 to titers at baseline. The 95% CI for GMT and GMFR were obtained based on a t-distribution of the log- transformed values.

Between-group ratio of GMT (Group H relative to G) was calculated. The GMTR at Day 28 and the two-sided 95% CIs were computed using an analysis of covariance with the vaccine group and age group ($18 - 54, \geq 55$) as the fixed effects and the titer at Day 0 (i.e., adjusted for intergroup variation in baseline [pre-vaccination] titers) as the covariate under two-sided type I error rate of 0.05. The mean difference between vaccine groups and the corresponding CI limits were then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs based on a t-distribution of log-transformed values and a pooled variance.

Superiority of the bivalent formulation compared to NVX-CoV2373 (Group H relative to G) for antibodies to Omicron BA.5 would be demonstrated if the lower-bound of the two-sided 95% CI was above 1.0. Non-inferiority of the bivalent formulation compared to NVX-CoV2373 (Group H relative to G) for antibodies to ancestral (Wuhan) strain would be demonstrated if the lower-bound of the two-sided 95% CI was above 0.67.

Seroresponse rates (SRRs) in neutralizing antibodies to the Omicron BA.5 subvariant at Day 28 following initial study vaccination were analyzed with two-sided exact binomial 95% CI based on the Clopper-Pearson method. The difference in SRRs between groups (expressed as Group H minus G) was calculated, with the 95% CI for the difference based

on the method of Miettinen and Nurminen. Non-inferiority would be demonstrated if the lower-bound of the two-sided 95% CI was above -5%.

Analysis of Safety

Similar to Study 311 Part 1.

Missing Data

Similar to Study 311 Part 1.

Interim Analysis

A formal analysis was carried out when the complete data were available to evaluate the primary objectives. At the time of the interim analysis, the applicant was unblinded at the participant level to prepare for regulatory submissions. At the request of FDA (CBER), an analysis was also conducted when data through the Day 189 phone call were available.

Multiplicity Adjustment

There was no adjustment necessary for as the set of 3 statistical hypotheses associated with the co-primary endpoints were tested simultaneously and all 3 null hypotheses needed to be rejected to declare success of the primary objective. Analyses of secondary and exploratory immunogenicity objectives/endpoints, as well as safety objectives/endpoints were descriptive.

Sample Size

The primary analysis population in Part 2 did not require a baseline negative anti-N result. Assuming 10% of participants were non-evaluable, a sample size of 250 participants per group for Groups F, G, and H provided approximately 89% power overall for the primary objective (comparing group H to G) when the null hypotheses were tested at one-sided 2.5% type I error level based on these assumptions:

1. For superiority of GMTs for Omicron BA.5 antibodies, a 1.5-fold difference in GMTs and a standard deviation of 0.5 for the log-transformed neutralization titers were assumed.
2. For non-inferiority of SRR for Omicron BA.5 antibodies, it is assumed the SRR in bivalent group was 50% and the SRR in prototype group was 28%.
3. For non-inferiority of GMTs for ancestral (Wuhan) antibodies, equivalent GMTs for the bivalent and prototype groups and a standard deviation of 0.5 for the log-transformed neutralization titers were assumed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 837 participants were screened in Part 2 of the study with 766 enrolled and randomly assigned to a treatment group (255 in Group F [NVX-CoV2540], 252 in Group G [NVX-CoV2373], and 259 in Group H [bivalent vaccine group]).

6.2.10.1.1 Demographics

The demographic and baseline characteristics in the safety set are described in Table 11. One subject from each of treatment groups F and G did not receive the vaccine and hence were not included in the safety analysis set. The demographic distributions were similar in all three arms. For all three treatment groups, proportion of Females (between 53.7% to 55.8%) were generally higher than proportion of males (between 44.2% to 46.3%) enrolled in the study. Most of the subjects were White (between 76.8% to 83.0%) across three treatment groups. The demographic characteristics were similar in the Per Protocol analysis Sets.

Table 11: Participant Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristics	**Group F NVX-CoV2540 (N=254)**	**Group G NVX-CoV2373 (N=251)**	**Group H NVX-CoV2373 + NVX-CoV2540 (N=259)**	**Total (N=764)**
Age (years)				
n	254	251	259	764
Mean (SD)	41.8 (12.89)	41.9 (13.58)	42.4 (12.48)	42.0 (12.97)
Median	43	43	43	43
Min – max	18 – 75	18 – 83	18 – 71	18 – 83
Age (years) Category, n (%)				
18 to 54	211 (83.1)	209 (83.3)	212 (81.9)	632 (82.7)
≥ 55	43 (16.9)	42 (16.7)	47 (18.1)	132 (17.3)
Sex, n (%)				
Male	113 (44.5)	111 (44.2)	120 (46.3)	344 (45.0)
Female	141 (55.5)	140 (55.8)	139 (53.7)	420 (55.0)
Race, n (%)				
White	195 (76.8)	205 (81.7)	215 (83.0)	615 (80.5)
Black or African American	1 (0.4)	1 (0.4)	0	2 (0.3)
Aboriginal Australian	4 (1.6)	3 (1.2)	8 (3.1)	15 (2.0)
Native Hawaiian or Other Pacific Islander	2 (0.8)	2 (0.8)	1 (0.4)	5 (0.7)
Asian	36 (14.2)	32 (12.7)	26 (10.0)	94 (12.3)
Mixed Origin	6 (2.4)	0	1 (0.4)	7 (0.9)
Other	10 (3.9)	8 (3.2)	6 (2.3)	24 (3.1)
Not Reported	0	0	2 (0.8)	2 (0.3)
Ethnicity, n (%)				

Characteristics	**Group F NVX-CoV2540 (N=254)**	**Group G NVX-CoV2373 (N=251)**	**Group H NVX-CoV2373 + NVX-CoV2540 (N=259)**	**Total (N=764)**
Australian	220 (86.6)	221 (88.0)	224 (86.5)	665 (87.0)
Aboriginal/Torres Strait Islanders	5 (2.0)	5 (2.0)	7 (2.7)	17 (2.2)
Hispanic or Latino	5 (2.0)	3 (1.2)	8 (3.1)	16 (2.1)
Not reported	13 (5.1)	13 (5.2)	11 (4.2)	37 (4.8)
Unknown	11 (4.3)	8 (3.2)	7 (2.7)	26 (3.4)
Missing	0	1 (0.4)	2 (0.8)	3 (0.4)
BMI (kg/m^2)				
n	252	250	256	758
Mean (SD)	28.59 (6.483)	28.76 (7.123)	28.48 (5.831)	28.61 (6.488)
Median	27.4	27.65	27.65	27.6
Min – max	16.9 – 59.4	16.2 – 70.6	16.0 – 51.8	16.0 – 70.6
BMI (kg/m^2) category, n (%)				
Underweight (< 18.0)	3 (1.2)	2 (0.8)	3 (1.2)	8 (1.0)
Normal (18.0 – 24.9)	79 (31.1)	85 (33.9)	75 (29.0)	239 (31.3)
Overweight (25.0 – 29.9)	83 (32.7)	73 (29.1)	85 (32.8)	241 (31.5)
Obese (≥ 30.0)	87 (34.3)	90 (35.9)	93 (35.9)	270 (35.3)
Missing	2 (0.8)	1 (0.4)	3 (1.2)	6 (0.8)
Previous COVID-19 Vaccine, n (%)				
Yes	254 (100)	251 (100)	259 (100)	764 (100)
Regimen of Previous COVID-19 Vaccine, n (%)				
3 doses	137 (53.9)	148 (59.0)	149 (57.5)	434 (56.8)
3 Moderna	5 (2.0)	1 (0.4)	2 (0.8)	8 (1.0)
3 Pfizer-BioNTech	107 (42.1)	110 (43.8)	121 (46.7)	338 (44.2)
1 Moderna + 2 Pfizer-BioNTech	24 (9.4)	36 (14.3)	26 (10.0)	86 (11.3)
2 Moderna + 1 Pfizer-BioNTech	1 (0.4)	1 (0.4)	0	2 (0.3)
4 doses	117 (46.1)	98 (39.0)	107 (41.3)	322 (42.1)
4 Moderna	0	1 (0.4)	0	1 (0.1)
4 Pfizer-BioNTech	72 (28.3)	53 (21.1)	66 (25.5)	191 (25.0)
1 Moderna + 3 Pfizer-BioNTech	34 (13.4)	27 (10.8)	24 (9.3)	85 (11.1)
2 Moderna + 2 Pfizer-BioNTech	11 (4.3)	17 (6.8)	17 (6.6)	45 (5.9)
3 Moderna + 1 Pfizer-BioNTech	0	0	0	0
5 doses	0	5 (2.0)	3 (1.2)	8 (1.0)
5 Moderna	0	0	0	0
5 Pfizer-BioNTech	0	4 (1.6)	2 (0.8)	6 (0.8)

Characteristics	Group F NVX-CoV2540 (N=254)	Group G NVX-CoV2373 (N=251)	Group H NVX-CoV2373 + NVX-CoV2540 (N=259)	Total (N=764)
1 Moderna + 4 Pfizer-BioNTech	0	1 (0.4)	1 (0.4)	2 (0.3)
2 Moderna + 3 Pfizer-BioNTech	0	0	0	0
3 Moderna + 2 Pfizer-BioNTech	0	0	0	0
4 Moderna + 1 Pfizer-BioNTech	0	0	0	0
Previous COVID-19 [1], n (%)				
Yes	13 (5.1)	15 (6.0)	18 (6.9)	46 (6.0)
No	241 (94.9)	236 (94.0)	241 (93.1)	718 (94.0)
Qualitative anti-N, n (%)				
Positive	194 (76.4)	183 (72.9)	205 (79.2)	582 (76.2)
Negative	60 (23.6)	68 (27.1)	53 (20.5)	181 (23.7)
Missing	0	0	1 (0.4)	1 (0.1)
PCR, n (%)				
Positive	7 (2.8)	5 (2.0)	5 (1.9)	17 (2.2)
Negative [2]	247 (97.2)	246 (98.0)	254 (98.1)	747 (97.8)
Anti-N / PCR [3], n (%)				
Positive	195 (76.8)	184 (73.3)	206 (79.5)	585 (76.6)
Negative	59 (23.2)	67 (26.7)	53 (20.5)	179 (23.4)
Time Between Last Previous COVID-19 Vaccine and First Dose of Study Investigational Vaccine (Days)				
N	254	251	259	764
Mean (SD)	347.8 (114.67)	354.5 (116.80)	358.4 (104.37)	353.6 (111.95)
Median	322.5	395	361	352.5
Min – max	103 – 679	92 – 626	103 – 537	92 – 679
Interval Between Last Previous COVID-19 Vaccine and First Dose of Study Investigational Vaccine, n (%)				
< 90 days	0	0	0	0
90 – 120 days	2 (0.8)	8 (3.2)	3 (1.2)	13 (1.7)
> 120 – 150 days	8 (3.1)	6 (2.4)	5 (1.9)	19 (2.5)
> 150 – 180 days	9 (3.5)	8 (3.2)	3 (1.2)	20 (2.6)
> 180 – 210 days	6 (2.4)	7 (2.8)	7 (2.7)	20 (2.6)
> 210 – 240 days	13 (5.1)	14 (5.6)	8 (3.1)	35 (4.6)
> 240 – 270 days	46 (18.1)	31 (12.4)	41 (15.8)	118 (15.4)
> 270 – 300 days	31 (12.2)	24 (9.6)	35 (13.5)	90 (11.8)
> 300 – 330 days	13 (5.1)	16 (6.4)	19 (7.3)	48 (6.3)

Characteristics	Group F NVX-CoV2540 (N=254)	Group G NVX-CoV2373 (N=251)	Group H NVX-CoV2373 + NVX-CoV2540 (N=259)	Total (N=764)
> 330 – 360 days	7 (2.8)	5 (2.0)	8 (3.1)	20 (2.6)
> 360 days	119 (46.9)	132 (52.6)	130 (50.2)	381 (49.9)

1. Previous COVID-19 was derived from programmatically checking Medical History records.
2. Four participants with missing PCR at baseline were imputed as negative.
3. Participants with either anti-N or PCR were reported.

Source: Table 19 of the Day 189 CSR of Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.10.1.3 Subject Disposition

The subject disposition information for Study 311 Part 2 is provided in Table 12. The dropouts were generally balanced across treatment arms.

Table 12: Summary of Participant Populations (All Randomized Participants Analysis Set)

Parameters	Group F NVX-CoV2540 n (%)	Group G NVX-CoV2373 n (%)	Group H Bivalent NVX-CoV2373+ NVX-CoV2540 n (%)	Total n (%)
All Randomized Participants Analysis Set	255 (100)	252 (100)	259 (100)	766 (100)
Excluded from Following Analysis Sets Not dosed	1 (0. 4)	1 (0.4)	0	2 (0.3)
FAS	254 (99.6)	251 (99.6)	259 (100)	764 (99.7)
SAF	254 (99.6)	251 (99.6)	259 (100)	764 (99.7)
Per-Protocol Analysis Set – Day 28 Visit				
Included	238 (93.3)	228 (90.5)	235 (90.7)	701 (91.5)
Excluded	16 (6.3)	23 (9.1)	24 (9.3)	63 (8.2)

Source: Adapted from Table 13 of the Day 189 CSR of Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

At Day 28, the bivalent vaccine (Group H) induced a superior NAb response in ID_{50} titers versus NVX-CoV2373 (Group G) against the Omicron BA.5 subvariant pseudovirus (GMT: 1100.9 [95% CI (913.9, 1326.1)] vs. 586.7 [95% CI [(480.9, 715.8)], respectively), with an adjusted GMTR of 2.0 (95% CI: 1.72, 2.37) where the LB of the two-sided 95% CI was > 1. (Table 13).

The bivalent vaccine (Group H) induced a non-inferior SRR against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 (Group G) at 40.4% (95% CI [34.1%, 47.0%]) and 12.3% (95% CI [8.3%, 17.3%]), respectively, at Day 28, with a difference in

SRRs of 28.1% (95% CI: 20.5%, 35.6%) where the LB of the two-sided 95% CI was > -5% (Table 13).

The bivalent vaccine (Group H) also induced a non-inferior response in ID_{50} titers versus NVX-CoV2373 (Group G) against the ancestral (Wuhan) pseudovirus (GMT: 2330.9 [95% CI (2007.1, 2707.0)] vs. 2361.1 [95% CI (2031.1, 2774.7)], respectively) at Day 28, with an adjusted GMTR of 1.0 (95% CI: 0.84, 1.18) where the LB of the two-sided 95% CI was > 0.67 (Table 14).

Table 13. Summary of Serum Neutralization Antibody Titers Against the Omicron BA.5 Pseudovirus Immunogenicity Endpoints (Per Protocol Pseudovirus Neutralization Assay Analysis Set)

	Group F NVX-CoV2540 N=238	**Group G NVX-CoV2373 N=228**	**Group H Bivalent NVX-CoV2373+ NVX-CoV2540 N=235**
Baseline			
n[a]	238	228	235
Median	392	401	360
Min - Max	18 - 27025	18 - 33971	18 - 35387
GMT	353.9	332	300.2
95% CI	288.0, 435.0	264.8, 416.1	243.4, 370.2
Day 28			
n[a]	238	228	235
Median	1602.5	677.5	1267
Min - Max	18 - 57888	18 - 38744	18 - 165841
GMT	1527.9	586.7	1100.9
95% CI	1275.8, 1829.9	480.9, 715.8	913.9, 1326.1
Adjusted GMT	1289.9	517.6	1042
95% CI	1130.1, 1472.4	452.5, 592.1	912.8, 1189.5
GMFR Between Visit and Baseline			
n[b]	238	228	235
Reference to Day 0	4.3	1.8	3.7
95% CI	3.7, 5.0	1.6, 2.0	3.2, 4.2
Seroresponse from Baseline			
n[c]	108	28	95
Percentage	45.4	12.3	40.4
95% CI	38.9, 51.9	8.3, 17.3	34.1, 47.0
Comparison Between Groups	**NVX-CoV2540 vs NVX-CoV2373**	**Bivalent (NVX-CoV2373 + NVX-CoV2540) vs NVX-CoV2373**	**NVX-CoV2540 vs Bivalent (NVX-CoV2373 + NVX-CoV2540) 1.2**
GMTR	2.5	2	1.2
95% CI	2.11, 2.94	1.72, 2.37	1.05, 1.48
Difference in SRR (%)	33.1	28.1	5
95% CI (%)	25.3, 40.6	20.5, 35.6	-4.0, 13.8

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and Day 28 titers available.

[c]Number of subjects achieving seroresponse.

Source: Table 14.2.1.1.1.s of the eSub 3 CSR Addendum to the 2019nCoV-311 Part 2 CSR submitted to BLA 125817/0.64.

Table 14. Comparison of Neutralizing Antibody Titers (ID50) Against the Ancestral (Wuhan) Pseudovirus at Day 28 After Initial Booster Vaccination with NVX-CoV2373 + NVX- CoV2540 and NVX-CoV2373 (Per-Protocol Pseudovirus Neutralization Assay Subset)

Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=235) GMT (95% CI)	**Group G NVX-CoV2373 (N=228) GMT (95% CI)**	**Adjusted GMTR (Bivalent / NVX-CoV2373) (95% CI)**	**Met Success Criteria**
2330.9 (2007.1, 2707.0)	2361.1 (2031.1, 2774.7)	1.0 (0.84, 1.18)	LB of 95% CI > 0.67 criterion: Yes

Source: Table 14.2.1.2.1.s of the eSub 3 CSR Addendum to the 2019nCoV-311 Part 2 CSR submitted to BLA 125817.64.

6.2.12 Safety Analyses

6.2.12.1 Solicited Local Adverse Events

The solicited injection-site adverse events are summarized in Table 15. The proportions of subjects reporting any solicited AE within 7 days post vaccination were similar post first and second booster vaccinations. Injection-site pain/tenderness was the most frequently reported injection-site adverse event for both post booster dose 1 (60.7% in Group F, 66.9% in Group G and 65.3% in Group H) and post booster dose 2 (60.5% in Group F, 59% in Group G and 62.9% in Group H). Post booster dose 1, the proportion of subjects who reported any injection-site were similar in Groups G and H, but were higher compared to group F.

Table 15. Summary of injection-site adverse events (Safety Analysis Set)

	Group F NVX-CoV2540 (N=252) n (%)	**Group G NVX-CoV2373 (N=251) n (%)**	**Group H Bivalent NVX-CoV2373+NVX-CoV2540 (N=259) n (%)**
Dose 1			
N	252	251	259
Any Solicited AE	187 (74.2)	196 (78.1)	204 (78.8)
Any Solicited AE of Grade 3	7 (2.8)	12 (4.8)	10 (3.9)
Any Solicited AE of Grade 4	0	0	0
Injection Site AEs			
Any Grade	153 (60.7)	168 (66.9)	169 (65.3)
Grade 3	4 (1.6)	2 (0.8)	2 (0.8)
Pain/tenderness			
Any Grade	153 (60.7)	166 (66.1)	169 (65.3)

Grade 3	4 (1.6)	2 (0.8)	2 (0.8)
Redness			
Any Grade	5 (2.0)	8 (3.2)	6 (2.3)
Grade 3	0	0	0
Swelling			
Any Grade	8 (3.2)	6 (2.4)	6 (2.3)
Grade 3	0	0	0
Dose 2			
N	238	234	245
Any Solicited AE	171 (71.8)	166 (70.9)	179 (73.1)
Any Solicited AE of Grade 3	7 (2.9)	15 (6.4)	14 (5.7)
Any Solicited AE of Grade 4	0	0	1 (0.4)
Injection Site AEs			
Any Grade	144 (60.5)	138 (59.0)	154 (62.9)
Grade 3	4 (1.7)	4 (1.7)	2 (0.8)
Grade 4	0	0	0
Pain/tenderness			
Any Grade	144 (60.5)	138 (59.0)	154 (62.9)
Grade 3	3 (1.3)	4 (1.7)	2 (0.8)
Redness			
Any Grade	8 (3.4)	3 (1.3)	3 (1.2)
Grade 3	1 (0.4)	0	0
Swelling			
Any Grade	6 (2.5)	2 (0.9)	2 (0.8)
Grade 3	0	0	0

Source: Tables 94 and 98 of the D189 CSR for Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.12.2 Solicited General Adverse Events

Solicited general adverse events within 7 days post vaccination are summarized in Table 16. The proportions of subjects reporting any solicited general AEs within 7 days post vaccination were generally similar post first and second booster vaccinations. Fatigue/malaise was the most frequently reported solicited general adverse event for both post booster dose 1 (42.1% in Group F, 41.0% in Group G and 37.5% in Group H) and post booster dose 2 (36.6% in Group F, 35.9% in Group G and 37.1% in Group H).

Table 16. Summary of Solicited General Adverse Events (Safety Analysis Set)

	Group F NVX-CoV2540 (N=252) n (%)	**Group G NVX-CoV2373 (N=251) n (%)**	**Group H Bivalent NVX-CoV2373+NVX-CoV2540 (N=259) n (%)**
Dose 1			
N	252	251	259
Any Grade	142 (56.3)	139 (55.4)	155 (59.8)
Grade 3	5 (2.0)	10 (4.0)	10 (3.9)
Fever			
Any Grade	2 (0.8)	2 (0.8)	4 (1.5)
Grade 3	0	0	1 (0.4)
Fatigue/malaise			
Any Grade	106 (42.1)	103 (41.0)	97 (37.5)

Grade 3	3 (1.2)	7 (2.8)	8 (3.1)
Muscle pain			
Any Grade	59 (23.4)	71 (28.3)	67 (25.9)
Grade 3	1 (0.4)	2 (0.8)	2 (0.8)
Joint pain			
Any Grade	18 (7.1)	20 (8.0)	19 (7.3)
Grade 3	0	1 (0.4)	1 (0.4)
Nausea/vomiting			
Any Grade	19 (7.5)	18 (7.2)	19 (7.3)
Grade 3	1 (0.4)	0	0
Headache			
Any Grade	73 (29.0)	73 (29.1)	74 (28.6)
Grade 3	4 (1.6)	2 (0.8)	3 (1.2)
Dose 2			
N	238	234	245
Systemic AEs			
Any Grade	124 (52.1)	117 (50.0)	131 (53.5)
Grade 3	5 (2.1)	12 (5.1)	13 (5.3)
Grade 4	0	0	1 (0.4)
Fever			
Any Grade	4 (1.7)	3 (1.3)	5 (2.0)
Grade 3	0	0	1 (0.4)
Grade 4	0	0	0
Fatigue/malaise			
Any Grade	87 (36.6)	84 (35.9)	91 (37.1)
Grade 3	4 (1.7)	10 (4.3)	10 (4.1)
Grade 4	0	0	1 (0.4)
Muscle pain			
Any Grade	64 (26.9)	59 (25.2)	60 (24.5)
Grade 3	2 (0.8)	3 (1.3)	4 (1.6)
Grade 4	0	0	0
Joint pain			
Any Grade	26 (10.9)	27 (11.5)	22 (9.0)
Grade 3	2 (0.8)	3 (1.3)	1 (0.4)
Grade 4	0	0	0
Nausea/vomiting			
Any Grade	11 (4.6)	12 (5.1)	19 (7.8)
Grade 3	0	0	1 (0.4)
Grade 4	0	0	0
Headache			
Any Grade	76 (31.9)	66 (28.2)	67 (27.3)
Grade 3	1 (0.4)	5 (2.1)	2 (0.8)
Grade 4	0	0	0

Source: Tables 94 and 98 of the D189 CSR for Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.12.3 Unsolicited General Adverse Events

Unsolicited adverse events post the first and second vaccinations are summarized in Tables 17 and 18, respectively. The numbers unsolicited AEs reported in these tables are based on the Day 189 CSR for study 311 Part 2. For this study, the data cutoff point was November 22, 2023. The proportions of subjects reporting any unsolicited AEs within 28 days post vaccination were generally similar post first and second booster vaccinations.

The incidence rates of unsolicited AEs through 28 days post first booster vaccination were slightly higher in Group G (25.9%) compared to Groups F (19.7%) and H (20.8%). In addition, 9.6% of the subjects reported MAAEs in Group G compared to 6.7% and 6.9% in Groups F and H respectively. The proportion of subjects who reported SAEs post Dose 2 was also higher in Group G (3.0%) compared to Groups F (0.8%) and H (0.4%).

One SAE of fourth cranial nerve palsy (originally classified by the Applicant as a non-serious AE but considered an SAE by the clinical reviewer) was reported by a 53-year-old White male in Group H on 14 days post first booster vaccination. This event is not included in Table 17.

Table 17: Overall Summary of Unsolicited Adverse Events from Initial Booster Vaccination with NVX-CoV2540, NVX-CoV2373, or Bivalent Vaccine Until Second Booster Vaccination or End of Study (Safety Analysis Set)

Parameters	**Group F NVX-CoV2540 (N=254) n (%)**	**Group G NVX-CoV2373 (N=251) n (%)**	**Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259) n (%)**
Unsolicited AEs through 28 days post initial booster			
Any TEAEs	50 (19.7)	65 (25.9)	54 (20.8)
Related TEAEs	2 (0.8)	5 (2.0)	7 (2.7)
Severe TEAEs	1 (0.4)	0	3 (1.2)
Related Severe TEAEs	0	0	1 (0.4)
Any MAAEs	17 (6.7)	24 (9.6)	18 (6.9)
Severe MAAEs	0	0	1 (0.4)
Unsolicited AEs until second booster vaccination or EoS			
Related Severe MAAEs	0	0	0
Related MAAEs	0	0	1 (0.4)
Related Serious MAAEs	0	0	0
Any Serious TEAEs	5 (2.0)	4 (1.6)	1 (0.4)
Related Serious TEAEs	1 (0.4)	0	0
Any AESIs (PIMMCs) [1]	1 (0.4)	1 (0.4)	2 (0.8)
Related AESIs (PIMMCs) [1]	1 (0.4)	1 (0.4)	0
Any AESIs (PIMMCs) [2]	0	0	1 (0.4)
Related AESIs (PIMMCs) [2]	0	0	0
Any AESIs (PIMMCs) [3]	1 (0.4)	1 (0.4)	2 (0.8)
Related AESIs (PIMMCs) [3]	1 (0.4)	1 (0.4)	0
Any AESIs: relevant to COVID-19	0	0	0
Any Myocarditis/Pericarditis	0	0	0
Any TEAEs Leading to Vaccination Discontinuation	1 (0.4)	2 (0.8)	0
Related TEAEs Leading to Vaccination Discontinuation	1 (0.4)	0	0
Any TEAEs Leading to Study Discontinuation	1 (0.4)	1 (0.4)	0

Parameters	Group F NVX-CoV2540 (N=254) n (%)	Group G NVX-CoV2373 (N=251) n (%)	Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259) n (%)
Related TEAEs Leading to Study Discontinuation	0	0	0

Note: MAAE, serious TEAE, PIMMC, AESI (COVID-19), and TEAEs leading to any discontinuation were reported through the second booster vaccination or data cutoff (Nov 22, 2023) whichever was earlier. Other TEAEs with start date within 28 days post first vaccination were reported.

[1] PIMMCs according to Protocol-defined Criteria or Investigator Reported in CRF.

[2] PIMMCs according to Protocol-defined Criteria.

[3] PIMMCs according to Investigator Reported in CRF.

Source: Table 102 of the D189 CSR for Study 311 Part 2 submitted to BLA 125817/0.15.

Table 18: Overall Summary of Unsolicited Adverse Events from Second Vaccination with NVX-CoV2540, NVX-CoV2373, or Bivalent Vaccine Until End of Study (Safety Analysis Set)

	Group F NVX-CoV2540 (N=254) n (%)	Group G NVX-CoV2373 (N=251) n (%)	Group H Bivalent NVX-CoV2373 + NVX-CoV2540 (N=259) n (%)
Unsolicited AEs through 28 days post second booster			
Any TEAEs	45 (18.9)	37 (15.8)	36 (14.7)
Related TEAEs	4 (1.7)	2 (0.9)	5 (2.0)
Severe TEAEs	1 (0.4)	2 (0.9)	0
Related Severe TEAEs	0	0	0
Any MAAEs	19 (8.0)	21 (9.0)	16 (6.5)
Severe MAAEs	1 (0.4)	2 (0.9)	0
Related Severe MAAEs	0	0	0
Unsolicited AEs from second booster until End of Study (EoS)			
Related MAAEs	1 (0.4)	1 (0.4)	2 (0.8)
Related Serious MAAEs	0	0	0
Any Serious TEAEs	2 (0.8)	7 (3.0)	2 (0.8)
Related Serious TEAEs	0	0	0
Any AESIs (PIMMCs) [1]	1 (0.4)	1 (0.4)	1 (0.4)
Related AESIs (PIMMCs) [1]	0	1 (0.4)	0
Any AESIs (PIMMCs) [2]	1 (0.4)	0	1 (0.4)
Related AESIs (PIMMCs) [2]	0	0	0
Any AESIs (PIMMCs) [3]	1 (0.4)	1 (0.4)	1 (0.4)
Related AESIs (PIMMCs) [3]	0	1 (0.4)	0
Any AESIs: relevant to COVID-19	0	1 (0.4)	0
Related AESIs: relevant to COVID-19	0	0	0
Any Myocarditis/Pericarditis	0	0	0
Any TEAEs Leading to Vaccination Discontinuation	0	0	0
Any TEAEs Leading to Study Discontinuation	0	0	0

Note: MAAE, serious TEAE, PIMMC, AESI (COVID-19), and TEAEs leading to any discontinuation were reported through the second booster vaccination or data cutoff (Nov 22, 2023) whichever was earlier. Other TEAEs with start date within 28 days post first vaccination were reported.

[1] PIMMCs according to Protocol-defined Criteria or Investigator Reported in CRF.

[2] PIMMCs according to Protocol-defined Criteria.

[3] PIMMCs according to Investigator Reported in CRF.

Source: Table 103 of the D189 CSR for Study 311 Part 2 submitted to BLA 125817/0.15.

6.2.12.3 Deaths

No deaths occurred in the study.

6.2.12.7 Dropouts and/or Discontinuations

From initial booster vaccination through End of Study, 1 (0.4%) participant (fourth nerve paralysis) in the NVX-CoV2540 group (Group F), 2 (0.8%) participants (1 with gastric sarcoma and 1 with pneumonia and asthma) in the NVX-CoV2373 group (Group G), and no participant in the bivalent vaccine group (Group H) reported unsolicited AEs leading to vaccination discontinuation.

6.3 Study 2019nCoV-313 Part 2

Study 2019nCoV-313 was a 2-part, Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 in adult participants ≥ 18 years of age previously vaccinated with mRNA COVID-19 vaccine (Part 1) and a single dose of NVX-CoV2601 in baseline SARS-CoV-2 seropositive, COVID-19 vaccine naïve adult participants ≥ 18 years of age (Part 2) in the U.S. and its territories. In Part 1 and Part 2 of the study, participants received NVX-CoV2601 on Day 0 and were followed for immunogenicity and safety through Day 180 with an interim analysis planned at Day 28. In this review, subjects enrolled in Part 1 and Part 2 of the study are referred to as the previously vaccinated and vaccine naïve subjects, respectively.

Part 1 of Study 2019nCoV-313 was initiated on September 07, 2023 (first participant screened) and completed enrollment on September 08, 2023. The co-primary objectives in Part 1 were 1) to determine if NVX-CoV2601 booster induced superior antibody responses to the Omicron XBB.1.5 subvariant compared to the antibody responses of a historical control of NVX-CoV2373 and 2) to determine if NVX-CoV2601 booster induced noninferior seroresponse rates (SRRs) to the Omicron XBB.1.5 subvariant compared to SRR of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations. Study 313 Part 1 was not reviewed separately in this memo as it does not provide effectiveness data to support the licensure of Nuvaxovid.

The purpose of inclusion of study 313 Part 2 in the review was to evaluate the performance of the vaccine in vaccine naïve subjects compared to the subjects who previously received

≥ 3 mRNA COVID-19 vaccinations. For this reason, primary and secondary objectives of the Part 1 of Study 313 were not evaluated during the process of the review of the BLA.

Part 2 of Study 2019nCoV-313 was initiated on September 18, 2023 (first participant screened) and completed enrollment on November 15, 2023. This memo focuses on the review of Part 2 of Study 2019nCoV-313.

6.3.1 Objectives

Co-Primary Objectives

1. To determine if a single dose of NVX-CoV2601 vaccine in SARS-Cov-2 seropositive COVID-19 vaccine naïve participants induced non-inferior SRR to the XBB.1.5 Omicron subvariant compared to that of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants.
2. To determine if a single dose of NVX-CoV2601 vaccine in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induced non-inferior antibody responses to the XBB.1.5 Omicron subvariant compared to a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants.

Secondary Objectives

1. To determine if the NVX-CoV2601 vaccine booster induced superior antibody responses to the Omicron XBB.1.5 subvariant compared to those of baseline titers.

2. To describe pseudovirus neutralization titers (ID_{50}) to the Omicron XBB.1.5 subvariant induced by the NVX-CoV2601 vaccine.

3. To describe IgG antibody responses to the Omicron XBB.1.5 subvariant induced by the NVX-CoV2601 vaccine.

4. To assess the overall safety of a single dose of the NVX-CoV2601 vaccine.

6.3.2 Design Overview

Part 2 of Study 2019nCoV-313 was a Phase 2/3, open-label, single-arm study evaluating the safety and immunogenicity of the Novavax Omicron XBB.1.5 subvariant vaccine adjuvanted with Matrix-M (NVX-CoV2601) in SARS-CoV-2 seropositive, vaccine naïve adults. Part 2 of the study aimed to investigate safety and immunogenicity of a single dose of NVX-CoV2601 in baseline SARS-CoV-2 seropositive, COVID-19 vaccine naïve participants to determine if it induced noninferior antibody responses compared to a single booster dose of NVX-CoV2601 in the previously COVID-19 mRNA vaccinated individuals participating in Part 1 of Study 2019nCoV-313.

6.3.3 Population

Medically stable male and nonpregnant female participants ≥ 18 years of age who were unvaccinated to SARS-CoV-2 and had a clinical history of COVID-19-like disease during the previous year were enrolled in this study.

6.3.4 Study Treatments or Agents Mandated by the Protocol

All subjects enrolled in this study received one dose of NVX-CoV2601 on Day 0. This vaccine was supplied as a pre-mixture solution for preparation for injection of SARS-CoV-2 rS (Omicron XBB.1.5 subvariant) at a concentration of 10μg/mL and Matrix-M adjuvant at a concentration of 100 μg/mL. The subjects received 0.5 mL injection volume at an antigenic dose of 5 μg/mL with 50 μg/mL Martix-M adjuvant. The vaccine was prepared and drawn into a syringe on the day of administration by a qualified member of study site personnel, and the vaccine was administered according to standard practice by qualified study site personnel.

6.3.6 Sites and Centers

The study was conducted at 30 sites in the U.S. and its territories.

6.3.7 Surveillance/Monitoring

Please refer to clinical review memo.

6.3.8 Endpoints and Criteria for Study Success

Co-primary Endpoints:

1. SRRs (proportion of seroconverted participants) in ID_{50} titers to the Omicron XBB.1.5 subvariant assessed at Day 28 following study vaccination.

2. ID_{50} GMTs to the Omicron XBB.1.5 subvariant assessed at Day 28 following study vaccination.

Secondary Endpoints:

Endpoint for 1st Secondary Objective

- Pseudovirus neutralization (ID_{50}) to the Omicron XBB.1.5 subvariant assessed at baseline and 28 days following study vaccination.

Endpoint for 2nd Secondary Objective

- Pseudovirus neutralization (ID_{50}) to the Omicron XBB.1.5 subvariant at relevant time points (Days 0, 28, and 180). Derived/calculated endpoints included GMFR and SRRs.

Endpoint for 3rd Secondary Objective

- Anti-S IgG GMCs (EU/mL) to the Omicron XBB.1.5 subvariant at relevant time points (Days 0, 28, and 180). Derived/calculated endpoints included GMFR and SRRs.

Endpoints for 4th Secondary Objective

- Incidence, duration, and severity of solicited local and systemic AEs for 7 days following vaccination.

- Incidence, severity, and relationship of unsolicited AEs through 28 days after vaccination.

- Incidence and severity of MAAEs attributed to study vaccine, AESIs (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and SAEs through Day 180 or EoS.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

- **Full Analysis Set** - The Full Analysis Set (FAS) included all participants who were enrolled and received at least 1 dose of study vaccine, regardless of protocol violations or missing data.
- **Safety Analysis Set** - The Safety Analysis Set included all participants who provided consent, were assigned to treatment, and received at least 1 dose of study vaccine. Participants in the Safety Analysis Set were analyzed as actually treated.
- **Per Protocol Pseudovirus Neutralization Assay Novavax Clinical Immunology Subset**- PP Pseudovirus Neutralization Assay Novavax Clinical Immunology Subset included all participants who received the full prescribed regimen of the study vaccine up to the visit according to protocol, were N antibody seropositive and PCR negative at baseline, had neutralization assay results at each time points and had no major protocol violations that were considered clinically relevant to impact immunogenicity response as determined prior to database lock.

Participants were excluded from the PP Analysis Set if:

- They had positive PCR at baseline.
- They did not receive the full prescribed regimen of the study vaccine up to the visit according to protocol.

- They had a major study deviation (e.g., administration of prohibited medication) affecting the immunogenicity response.
- They had received COVID-19 vaccine before study vaccination.
- They were anti-N negative at baseline.
- Their anti-N result was missing at baseline.

Analysis of Immunogenicity

The comparison of a single dose of NVX-CoV2601 vaccine booster in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants versus a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants with respect to antibody responses was carried out using an analysis of covariance (ANCOVA) model. The model included antibody responses (log-transformed) as the dependent variable, the groups of participants as a fixed effect, and the baseline antibody response as a covariate. The mean difference between the vaccine groups along with its two-sided 95% CI was exponentiated to obtain the ratio of ID50 GMTs and the corresponding 95% CIs. Non-inferiority would be achieved if the LB of the two-sided 95% CI exceeded 0.67.

Seroresponse rates (SRRs) in neutralizing antibodies to the Omicron XBB.1.5 subvariant at Day 28 following initial study vaccination was calculated. Two-sided exact binomial 95% CIs were calculated using the Clopper-Pearson method. The difference in SRRs elicited by a single dose of NVX-CoV2601 vaccine booster in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants and that elicited by a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants was computed along with its corresponding two-sided 95% CI at Day 28. The two-sided 95% CI was based on the method of Miettinen and Nurminen. The SRR rate elicited by a single dose of NVX-CoV2601 vaccine booster in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants would be declared NI to that elicited by a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants if the LB of the two- sided 95% CI exceeded -10%.

Analysis of Safety

Similar to Study 311 Part 1 and Part 2.

Missing Data

Similar to Study 311 Part 1 and Part 2.

Interim Analysis

There were 2 planned analyses in this study, the Day 28 interim analysis and the Day 180 final analysis.

Multiplicity Adjustment

The applicant needed to meet the noninferiority criteria for both the GMTR and SRR endpoints at Day 28. Therefore, no multiplicity adjustment was needed.

Sample Size

The study sample size was determined based on statistical power calculation for the GMTR endpoint. Assuming an SD of 0.6 for log10-transformed neutralization titers based on data from previous studies, a 25% attrition rate, and an overall one-sided Type I error rate of 2.5%, a sample size of 330 per group would provide at least 95% power to demonstrate NI of the NVX-CoV2601 vaccine to the historical control. Of note, the per-protocol analysis set in Study 313 Part 1 included 305 participants.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 670 healthy adult subjects ≥ 18 years of age were enrolled in Study 2019nCoV-313. Among these, 332 previously vaccinated subjects were enrolled in Part 1 of the study and 338 vaccine naïve subjects were enrolled in Part 2 of the study.

6.3.10.1.1 Demographics

The demographic and baseline characteristics in the safety analysis set are described in Table 19. The proportion of subjects in the 18-54 years age group was higher in the vaccine naïve group (84%) compared to previously vaccinated group (53%). The racial combination in the vaccine naïve group was different compared to the previously vaccinated group as there were more Black and African American and fewer white participants in the vaccine naïve group versus the previously vaccinated group. The demographic characteristics were similar in the per protocol analysis set compared to the safety analysis set.

Table 19: Summary of Demographic Results (Safety Analysis Set)

	Vaccine Naïve (Part 2) N=338	**Previously Vaccinated (Part 1) N=332**
Age (years)		
Mean (SD)	40.5 (13.11)	52.0 (16.07)
Median	38	53
Min – max	18 – 75	18 – 89
Age (years) category, n (%)		
18 to 54	284 (84.0)	176 (53.0)
≥ 55	54 (16.0)	156 (47.0)
Sex, n (%)		
Male	148 (43.8)	124 (37.3)
Female	190 (56.2)	208 (62.7)
Race, n (%)		
White	167 (49.4)	248 (74.7)
Black or African American	147 (43.5)	53 (16.0)

	Vaccine Naïve (Part 2) N=338	**Previously Vaccinated (Part 1) N=332**
American Indian or Alaskan Native	6 (1.8)	6 (1.8)
Native Hawaiian or Other Pacific Islander	1 (0.3)	2 (0.6)
Asian	2 (0.6)	12 (3.6)
Multiple	5 (1.5)	3 (0.9)
Other	3 (0.9)	1 (0.3)
Unknown	0	1 (0.3)
Not Reported	7 (2.1)	6 (1.8)
Ethnicity, n (%)		
Hispanic or Latino	87 (25.7)	67 (20.2)
Not Hispanic or Latino	249 (73.7)	261 (78.6)
Not Reported	2 (0.6)	4 (1.2)
BMI (kg/m^2)		
n	338	331
Mean (SD)	31.61 (10.071)	30.98 (7.805)
Median	29.55	29.8
Min – max	11.5 – 72.6	16.6 – 64.5
BMI (kg/m^2) category, n (%)		
Underweight (< 18.0)	8 (2.4)	2 (0.6)
Normal (18.0 – 24.9)	77 (22.8)	72 (21.7)
Overweight (25.0 – 29.9)	90 (26.6)	95 (28.6)
Obese (≥ 30.0)	163 (48.2)	162 (48.8)
Missing	0	1 (0.3)
Previous COVID-19 [3], n (%)		
Yes	335 (99.1)	5 (1.5)
Qualitative anti-N, n (%)		
Positive	315 (93.2)	234 (70.5)
Negative	23 (6.8)	98 (29.5)
PCR, n (%)		
Positive	5 (1.5)	5 (1.5)
Negative	333 (98.5) [1]	327 (98.5) [2]
Anti-N / PCR [3], n (%)		
Positive	315 (93.2)	234 (70.5)
Negative	23 (6.8)	98 (29.5)

Abbreviations: anti-N = anti-nucleocapsid; BMI = body mass index; COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; NA = not available; NVX-CoV2601 = 5 µg SARS-CoV-2 rS (Omicron XBB.1.5 subvariant) with 50 µg Matrix-M adjuvant; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS = severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD = standard deviation.

1. 5 participants with missing PCR at baseline were imputed as negative.

2. 2 participants with missing PCR at baseline were imputed as negative.

3. Participants with either anti-N or PCR were reported

Source: Table 15 of the Final CSR of Study 313 Part 2 submitted to BLA 125817/0.45.

6.1.10.1.3 Subject Disposition

The subject disposition information for Study 313 is provided in Table 20. The proportions of subjects retained in the per protocol set from the randomized set were similarly high in Part 1 and Part 2.

Table 20: Subject Dispositions (All Enrolled/Randomized Participants Analysis Set)

	Vaccine Naïve (Part 2) N=338 n (%)	**Previously Vaccinated (Part 1) N=332 n (%)**
Full Analysis Set	338 (100)	332 (100)
Safety Analysis Set	338 (100)	332 (100)
PP Analysis Set - Day 28 visit		
Included	306 (90.5)	309 (93.1)
Excluded	32 (9.5)	23 (6.9)
Baseline anti-N result negative	23 (6.8)	NA
Baseline positive PCR result	5 (1.5)	5 (1.5)
Protocol deviation	5 (1.5)	18 (5.4)
Baseline anti-N result missing	0	NA
COVID-19 vaccine received before study vaccination	0	NA

Source: Adapted from Table 12 of the Final CSR of Study 313 Part 2 submitted to BLA 125817/0.45.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoints

The analysis results of the primary immunogenicity endpoints are summarized in Table 21. The first primary endpoint of the nAb response against the Omicron XBB.1.5 pseudovirus following a single dose NVX-CoV2601 in COVID-19 vaccine naïve participants compared to that of NVX-CoV2601 booster in previously COVID-19 mRNA vaccinated participants showed an adjusted GMTR (Vaccine naïve/previously vaccinated) of 1.8 with a two-sided 95% CI of (1.43, 2.20). The noninferiority criterion was met as the LB of the two-sided 95% CI for the GMTR exceeded 0.67.

The second primary endpoint was the SRR for a single dose NVX-CoV2601 in COVID-19 vaccine naïve participants (Part 2) compared to that of NVX-CoV2601 booster in previously COVID-19 mRNA vaccinated participants (Part 1). The SRRs were 74.3% (68.9%, 79.3%) and 64.3% (58.6%, 69.6%) in Part 2 and Part 1, respectively, at Day 28. The difference in the SRRs (Part 2 minus Part 1) was 10%, with a two-sided 95% CI (2.6%,

17.4%). The LB of the two-sided 95% CI was greater than -10.0%, which met the noninferiority criterion.

Table 21: Summary of Primary Immunogenicity Endpoints (PP Pseudovirus Neutralization Assay Novavax Clinical Immunology Subset)

	Vaccine Naïve (Part 2)	**Previously Vaccinated (Part 1)**
N	288	305
GMT	1303.7 (1087.4, 1563.0)	955.5 (814.0, 1121.4)
Adjusted GMT	1491.5 (1277.5, 1741.4)	841.4 (723.9, 978.0)
GMR (Vaccine Naïve /Previously Vaccinated)	1.8 (1.4, 2.2)	
Seroresponse Rate (%)	74.3 (68.9, 79.3)	64.3 (58.6, 69.6)
Difference in SRRs (Vaccine Naïve – Previously Vaccinated)	10.0 (2.6, 17.4)	

Source: Table 16 of the Final CSR of Study 313 Part 2 submitted to BLA 125817/0.45.

Reviewer's Comment: Due to the demographic imbalance between the subjects included in the two arms of the study, I conducted a sensitivity analysis for GMR using inverse probability treatment weighting method to adjust for the imbalance. The sensitivity analysis provided similar conclusions.

6.3.11.2 Analyses of Secondary Endpoints

The secondary objectives were to evaluate the pseudovirus neutralizations at Day 0, Day 28 and D180 among all the subjects enrolled in Study 313 Part 2. Table 22 summarizes the serum neutralizing antibody titers (ID_{50}) against Omicron XBB.1.5 Pseudovirus. GMFR from Day 0 to Day 28 was 19.3 (95% CI: 15.7, 23.7) and from Day 0 to Day 180 was 4.7 (95% CI: 3.8, 5.7). SRR from Day 0 to Day 28 was 74.3% (95% CI: 68.9%, 79.3%) and from Day 0 to Day 180 was 45.0% (95% CI: 38.8%, 51.4%). The GMFR and SRR from baseline to Day 28 and Day 180 were generally higher in the ≥ 55 years age group compared to the 18–54 years age group.

Table 22: Summary of Serum Neutralizing Antibody Titers (ID50) against Omicron XBB.1.5 Pseudovirus (Per-Protocol Pseudovirus Neutralization Assay Novavax Clinical Immunology Subset)

	Vaccine Naïve (Part 2) N=305 ≥18 Years	**Vaccine Naïve (Part 2) N=261 18-54 Years**	**Vaccine Naïve (Part 2) N=44 ≥ 55 Years**
Day 0 (Baseline)			
n[a]	305	261	44
GMT (ID_{50})	67 (56.6, 79.3)	64.9 (54.2, 77.6)	81.3 (49.4, 133.9)
Day 28			
n[a]	290	247	43

	Vaccine Naïve (Part 2) N=305 ≥18 Years	**Vaccine Naïve (Part 2) N=261 18-54 Years**	**Vaccine Naïve (Part 2) N=44 ≥ 55 Years**
GMT (ID_{50})	1296.7 (1082.6, 1553.2)	1201.4 (988.6, 1406.1)	2009.9 (1250.4, 3231.0)
Day 180			
n[a]	254	216	38
GMT	303.6 (258.5, 356.4)	277 (233.8, 328.1)	511 (323.4, 807.2)
GMFR between Day 28 and Baseline			
n[b]	288	245	43
Reference to Baseline (CI)	19.3 (15.7, 23.7)	18.4 (14.7, 23.0)	25.6 (15.0, 43.5)
GMFR Between Day 180 and Baseline			
n[c]	251	213	38
Reference to Baseline (CI)	4.7 (3.8, 5.7)	4.4 (3.6, 5.5)	6.3
SRR from Baseline to Day 28			
n[d]	214	179	35
Percentage (CI)	74.3 (68.9, 79.3)	73.1 (67.0, 78.5)	81.4 (66.6, 91.6)
SRR from Baseline to Day 180			
n[d]	113	92	21
Percentage (CI)	45 (38.8, 51.4)	43.2 (36.4, 50.1)	55.3 (38.3, 71.4)

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and day 28 titers available.

[c]Number of subjects with both baseline and day 180 titers available.

[d]Number of subjects achieving seroresponse from baseline

Source: Adapted from Tables 17 and 18 of the Final CSR of Study 313 Part 2 submitted to BLA 125817/0.45.

Following a single dose of NVX-CoV2601 among all the subjects enrolled in Study 313 Part 2, anti-recombinant spike (rS) IgG antibody GMEU against the Omicron XBB.1.5 rS protein increased from Day 0 (5188.1 EU/mL [95% CI: 4342.1, 6198.9]) to Day 28 (46961.6 EU/mL [95% CI: 42046.8, 52450.9]) and Day 180 (14606.7 EU/mL [95% CI: 12772.3, 16704.6]) (Table 23). GMFRs from Day 0 to Day 28 and from Day 0 to Day 180 were 9.0 (95% CI: 7.6, 10.7) and 2.8 (95% CI: 2.4, 3.4), respectively. SRRs were 68.4% (95% CI: 62.7%, 73.7%), and 38.2% (95% CI: 32.2%, 44.6%) at Day 28 and Day 180, respectively. The SRR from baseline and GMFR from baseline were generally similar among 18-54 years age group compared to ≥ 55 years age group.

Table 23: Summary of Serum Anti-rS IgG Antibody Levels at Day 28 and Day 180 against Omicron XBB.1.5 Subvariant Spike Protein following Single Dose vaccination (Per-Protocol Anti-S Protein Serology Subset)

	Vaccine Naïve (Part 2) N=305 ≥18 Years	**Vaccine Naïve (Part 2) N=261 18-54 Years**	**Vaccine Naïve (Part 2) N=44 ≥ 55 Years**
Day 0 (Baseline)			
n[a]	305	261	44
GMEU (Geometric Mean EU/mL)	5188.1 (4342.1, 6198.9)	5067 (4181.3, 6140.3)	5967.9 (3656.2, 9741.3)
Day 28			
n[a]	290	247	43
GMEU	46961.6 (42046.8, 52450.9)	45909.9 (40788.4, 51674.4)	53487.2 (38976.8, 73399.4)
Day 180			
n[a]	254	216	38
GMEU (Geometric mean EU/mL)	14606.7 (12772.3, 16704.6)	14087.0 (12162.8, 16315.5)	17947.1 (12823.7, 25117.6)
GMFR Between Day 28 and Baseline			
n[b]	288	245	43
Reference to Baseline	9 (7.6, 10.7)	9 (7.4, 10.9)	9.3 (6.4, 13.6)
GMFR Between Day 180 and Baseline			
n[c]	251	213	38
Reference to Baseline	2.8 (2.4, 3.4)	2.8 (2.3, 3.4)	2.9 (1.9, 4.5)
SRR from Baseline to Day 28			
n[d]	197	166	31
Percentage	68.4 (62.7, 73.7)	67.8 (61.5, 73.6)	72.1 (56.3, 84.7)
SRR from Baseline to Day 180			
n[d]	96	80	16
Percentage	38.2 (32.2, 44.6)	37.6 (31.0, 44.4)	42.1 (26.3, 59.2)

[a]Number of subjects for whom titer results available at the specific timepoint.

[b]Number of subjects with both baseline and day 28 titers available.

[c]Number of subjects with both baseline and day 180 titers available.

[d]Number of subjects achieving seroresponse from baseline.

Source: Adapted from Tables 19 and 20 of the Final CSR of Study 313 Part 2 submitted to BLA 125817/0.45.

6.3.12 Safety Analyses

6.3.12.1 Solicited Local Adverse Events

Safety analyses were performed on the safety analysis set and both Part 1 and Part 2 safety results are included in this memo. Solicited local adverse events reported within 7 days (i.e. Days 0-6) post-vaccination period for Parts 1 and 2 of the study are summarized in Table 24. Frequencies and proportions of solicited local injection-site AEs were generally higher in subjects who were previously vaccinated (56.9%) than the vaccine naïve subjects (41.4%). Injection-site pain/tenderness was the most common solicited local AE, reported by approximately 41.4% of the subjects in the vaccine naïve group and 56.0% of the subjects in the previously vaccinated group.

Table 24: Summary of Solicited Local Injection Site (Safety Analysis Set)

	Vaccine Naïve (Part 2) N=338 n (%)	**Previously Vaccinated (Part 1) N=332 n (%)**
Any solicited local injection site TEAE		
Any Grade	140 (41.4)	189 (56.9)
≥ Grade 3	3 (0.9)	1 (0.3)
Pain		
Any Grade	85 (25.1)	98 (29.5)
≥ Grade 3	2 (0.6)	0
Tenderness		
Any Grade	129 (38.2)	171 (51.5)
≥ Grade 3	3 (0.9)	1 (0.3)
Pain/tenderness		
Any Grade	140 (41.4)	186 (56.0)
≥ Grade 3	3 (0.9)	1 (0.3)
Redness		
Any Grade	4 (1.2)	6 (1.8)
≥ Grade 3	0	0

Source: Adapted from Table 21 of the Final CSR of 2019nCoV-313 Part 2 submitted to BLA 125817/0.45.

6.3.12.2 Solicited Systemic Adverse Events

Solicited systemic adverse events reported during the 7-day (i.e. Days 0-6) post-vaccination period are summarized in Table 25. The proportions of subjects who experienced a specific solicited systemic adverse event were generally similar among participants who were vaccine naïve and who were previously vaccinated. Most frequently reported systemic AEs include fatigue/malaise (29.0% and 32.8% in vaccine naïve and previously vaccinated participants respectively), muscle pain (31.4% and 29.2% in vaccine naïve and previously vaccinated participants respectively) and headache (27.2% and 22.3% in vaccine naïve and previously vaccinated participants respectively).

Table 25: Summary of Solicited Systemic Adverse Events (Safety Analysis Set)

	Vaccine Naïve (Part 2) N=338 n (%)	**Previously Vaccinated (Part 1) N=332 n (%)**
Any solicited systemic TEAE		
Any Grade	164 (48.5)	158 (47.6)
Grade 3	7 (2.1)	4 (1.2)
Fever		
Any Grade	3 (0.9)	2 (0.6)
Grade 3	0	0
Fatigue		
Any Grade	80 (23.7)	97 (29.2)
Grade 3	3 (0.9)	1 (0.3)
Malaise		
Any Grade	48 (14.2)	54 (16.3)
Grade 3	3 (0.9)	3 (0.9)
Fatigue/malaise		
Any Grade	98 (29.0)	109 (32.8)
Grade 3	4 (1.2)	3 (0.9)
Muscle Pain		
Any Grade	106 (31.4)	97 (29.2)
Grade 3	4 (1.2)	1 (0.3)
Joint pain		
Any Grade	44 (13.0)	39 (11.7)
Grade 3	2 (0.6)	0
Nausea/vomiting		
Any Grade	42 (12.4)	25 (7.5)
Grade 3	2 (0.6)	0
Headache		
Any Grade	92 (27.2)	74 (22.3)
Grade 3	3 (0.9)	2 (0.6)

Source: Adapted from Table 24 of the CSR of 2019nCoV-313 Part 2 submitted to BLA 125817/0.45.

6.3.12.3 Unsolicited Adverse Events

A summary of unsolicited AEs is summarized in Table 26. The proportion of subjects who experienced at least one TEAE through 28 days post vaccination among subjects who were previously vaccinated (8.7%) was slightly higher than among the participants who were vaccine naïve (5.3%). A total of 4 (1.2%) vaccine naïve (Part 2) and 5 (1.5%) previously vaccinated (Part 1) subjects reported SAEs for the duration of the study.

Table 26: Summary of Unsolicited Adverse Events (Safety Analysis Set)

	Vaccine Naïve (Part 2) N=338 n (%)	**Previously Vaccinated (Part 2) N=332 n (%)**
Unsolicited TEAEs reported through 28 days after single dose or booster vaccination		
Any unsolicited TEAE	18 (5.3)	30 (9.0)
Treatment-related	1 (0.3)	4 (1.2)
Severe	1 (0.3)	2 (0.6)
Treatment-related severe	0	0
Any MAAE	8 (2.4)	14 (4.2)
Severe	1 (0.3)	2 (0.6)
Unsolicited TEAEs reported through end of study		
Any treatment-related MAAE	0	1 (0.3)
Severe	0	0
Serious	0	0
Any SAE	5 (1.5)	4 (1.2)
Treatment-related	0	0
Any AESIs (PIMMCs)	0	0
Any AESIs: Relevant to COVID-19	0	0
Any Myocarditis/Pericarditis	0	0
Any TEAE Leading to Study Discontinuation	1 (0.3)	0

Related MAAE, Serious TEAE, PIMMC, AESI (COVID-19), myocarditis/pericarditis, and TEAEs leading to any discontinuation are reported through end of study. Other TEAE categories are reported through 28 days after the study vaccination.
Source: Adapted from Table 27 submitted to BLA 125817/0.98.

6.3.12.3 Deaths

One vaccine naïve participant died due to fentanyl overdose (b) (6) days after receiving the vaccination and was assessed by the investigator and the applicant as not related to the study vaccine.

6.3.12.7 Dropouts and/or Discontinuations

In Study 313 Part 2, among the vaccine naïve subjects, 1 subject had an TEAE leading to study discontinuation (overdose) after single dose vaccination of NVX-CoV2601. This event resulted in death and is described in Section 6.3.12.3. No TEAEs leading to study discontinuation were reported among previously vaccinated participants in Part 1.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

Please refer to (b) (6) memo regarding the integrated Summary of Safety.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues identified.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This statistical review memo focuses on clinical studies 2019nCoV-311 Part 1 (311 Part 1), 2019nCoV-311 Part 2 (311 Part 2), and 2019nCoV-313 Part 2 (313 Part 2).

Study 311 was a two-part, phase 3, randomized, observer-blind study to evaluate the safety and immunogenicity of omicron subvariant and bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines. This study provided evidence to support the use of Nuvaxovid as a heterologous booster.

Study 311 Part 1 evaluated a single booster dose of monovalent NVX-CoV2515 (SARS-CoV-2 BA.1 [Omicron] subvariant), monovalent NVX-CoV2373 (Wuhan-Hu-1), and bivalent prototype and Omicron subvariant vaccine (site mixed NVX-CoV2373 and NVX-CoV2515) in previously vaccinated adults 18 to 64 years of age (inclusive) in Australia.

The primary objective of Study 311 Part 1 was to determine whether NVX-CoV2515 (Group C) induced superior antibody responses to the Omicron BA.1 subvariant compared to the antibody responses induced by NVX-CoV2373 (Group D) in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype vaccines.

The geometric mean of microneutralization (MN_{50}) titers at Day 14 were 130.8 (95% CI: 109.2, 156.7) vs. 83.9 (95% CI: 69.6, 101.2) for NVX-CoV2515 and NVX-CoV2373, respectively, resulting in an adjusted Geometric Mean Titer Ratio (GMTR) of 1.6 (95% CI: 1.33, 2.03), meeting the superiority success criterion of the LB of the two-sided 95% CI being >1. Seroresponse rates (SRRs) were 73.4% (95% CI: 64.7%, 80.9%), versus 50.9% (95% CI: 41.4%, 60.3%), in NVX-CoV2515 and NVX-CoV2373 groups, respectively, resulting in a difference of 22.5% (95% CI: 10.3%, 34.2%) in SRRs, meeting the success criterion of LB of the 95% CI being > -5%.

The safety and reactogenicity profiles of the treatment groups were generally similar. Of note, 1(1.6%), 2 (3.3%), 8 (2.8%), 4 (1.5%) and 4 (1.5%) of the participants reported serious adverse events (SAEs) till the end of the study in Groups A, B, C, D and E respectively. All SAEs (including fatalities) reported in this study were assessed by the investigator as not causally related to vaccination.

Study 311 Part 2 evaluated the safety and immunogenicity of two booster doses of monovalent NVX-CoV2540 (SARS-CoV-2 BA.5 [Omicron] subvariant), monovalent NVX-CoV2373 (Wuhan-Hu-1), and bivalent prototype and Omicron BA.5 subvariant vaccine (site mixed NVX-CoV2373 and NVX-CoV2540) in previously vaccinated adults 18 years of age or older in Australia. In this study, participants who were previously vaccinated with ≥ 3 doses of Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days were planned to be randomized to receive NVX-CoV2540 (Group F), NVX-CoV2373 (Group G) or NVX-CoV2373+NVX-CoV2540 (Group H). The primary objective of the study was to evaluate whether the bivalent vaccine (NVX-CoV2373+NVX-CoV2540) induced superior antibody responses compared to the antibody response induced by NVX-CoV2373.

The success criteria for all 3 co-primary endpoints were achieved in Part 2 of the study. Briefly, the bivalent vaccine induced a superior NAb response against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 with GMTs of 1100.9 (95% CI: 913.9, 1326.1) vs. 586.7 (95% CI: 480.9, 715.8) at Day 28, resulting in an adjusted GMTR of 2.0 (95% CI: 1.72, 2.37) where the lower bound (LB) of the two-sided 95% CI was > 1, meeting the superiority criterion. In addition, the bivalent vaccine induced a non-inferior SRR against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 (40.4% [95% CI: 34.1%, 47.0%] vs. 12.3% [95% CI: 8.3% 17.3%], respectively) at Day 28, with a difference in SRRs of 28.1% (95% CI: 20.5%, 35.6%) where the LB of the two-sided 95% CI was > -5%, meeting the non-inferiority criterion. Lastly, the bivalent vaccine induced a non-inferior response versus NVX-CoV2373 in regard to the induction of NAbs against the ancestral (Wuhan) pseudovirus (GMTs 2230.9 [95% CI: 2007.1, 2707.0] versus 2361.1 [95% CI: 2031.1, 2744.7], respectively) at Day 28, with an adjusted GMTR of 1.0 (95% CI: 0.84, 1.18) where the LB of the two-sided 95% CI was > 0.67, meeting the non-inferiority criterion.

The safety and reactogenicity profiles of the treatment groups were generally similar. One (0.4%) participant reported a Grade 4 solicited systemic adverse event (AE) (fatigue/malaise) in the bivalent vaccine group. From the first vaccination until the data cutoff date of November 22, 2023, 7 (2.8%), 10 (4.0%) and 3 (0.8%) participants reported SAEs in Groups F, G and H, respectively. One participant had a related serious adverse event (SAE) of fourth nerve paralysis that occurred after the initial vaccination of NVX-CoV2540 (Group F) and did not receive the second booster dose.

Study 313 was a two-part, Phase 2/3, Open-Label study to evaluate the safety and immunogenicity of a single dose of XBB.1.5 (Omicron subvariant), NVX-CoV2601 vaccine in previously mRNA COVID-19 vaccinated and baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants aged 18 years and older in the U.S.

In Study 313 Part 1, 332 participants who were previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer/BioNTech prototype monovalent and/or BA.4/5-containing bivalent COVID-19 vaccines with the last dose administered ≥ 90 days prior to study vaccination were administered with NVX-CoV2601 vaccine. The primary objective of this

part of the study to determine if the NVX-CoV2601 booster vaccine induced superior antibody responses to the XBB.1.5 subvariant compared to those of a historical control from clinical Study 311 Part 2 who received NVX-CoV2373 (Group G) was achieved. Study 313 Part 1 was not reviewed separately in this memo as it does not provide effectiveness data to support the licensure of Nuvaxovid.

In Study 313 Part 2, 338 vaccine native participants with a clinical history of COVID-19-like illness received one dose of NVX-CoV2601 vaccine. The primary objective of the study was to evaluate whether a single dose of NVX-CoV2601 vaccine in vaccine naïve participants induced noninferior antibody responses and SRRs to the Omicron XBB.1.5 subvariant compared to the historical control of subjects who were enrolled in Study 313 Part 1. Part 2 of the study provided data to support the use of Nuvaxovid in vaccine naïve participants with evidence of prior SARS-CoV-2 infection.

The geometric mean of nAb titers against Omicron XBB.1.5 pseudovirus following a single dose of NVX-2601 were 1303.7 (95% CI: 1087.4, 1563.0) and 955.5 (95% CI: 814.0, 1121.4) in vaccine naïve and previously vaccinated participants, respectively, resulting in an adjusted GMTR of 1.8 (95% CI: 1.4, 2.2), meeting the noninferiority success criterion of the LB of the two-sided 95% of GMTR being > 0.67. The SRRs were 74.3% (95% CI: 68.9%, 79.3%) and 64.3% (95% CI: 58.6%, 69.6%) in vaccine naïve and previously vaccinated participants, respectively, resulting in a difference in SRRs of 10% (95% CI: 2.6%, 17.4%), meeting the noninferiority criterion of the LB of the 95% CI being >-10%.

The safety and reactogenicity profiles were generally similar in both vaccine naïve and previously vaccinated groups. Of note, 5 (1.5%) and 4 (1.2%) of the participants in vaccine naïve and previously vaccinated groups reported SAEs. None of these SAEs were assessed as related to the study vaccination by the investigator.

There were no cases of myocarditis/pericarditis reported in Studies 311 Part 1, 311 Part 2, 313 Part 1 and 313 Part 2.

10.2 Conclusions and Recommendations

Study 311 Part 1 demonstrated that NVX-CoV2515 induced superior immune response to NVX-CoV2373 among subjects who previously received ≥ 3 doses of mRNA COVID-19 vaccines. Study 311 Part 2 demonstrated that Bivalent NVX-CoV2373+NVX-CoV2540 induced superior NAb response to NVX-CoV2373 against Omicron BA.5 subvariant pseudovirus, and induced noninferior NAb response to NVX-CoV2373 against Wuhan strain among subjects who previously received ≥ 3 doses of mRNA COVID-19 vaccines. Study 313 Part 2 demonstrated that a single dose of NVX-CoV2601 induced noninferior immune response in SARS-CoV-2 seropositive, vaccine naïve participants compared to subjects who previously received at least 3 doses of mRNA COVID-19 vaccines.