BLA Clinical Review Memorandum

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Applicant	Novavax, Inc
Proper Name	COVID-19 Vaccine, Adjuvanted
(Proposed) Trade Name	Nuvaxovid
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	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 in individuals 12 years of age and older to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Orphan Designated (Yes/No)	No

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GLOSSARY

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	Biologics License Application
BMI	body mass index
C-VIPER	COVID-19 Vaccines International Pregnancy Exposure Registry
CABG	coronary artery bypass graft
CAD	coronary arterial disease
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPR	cardiopulmonary resuscitation
CRO	clinical research organization
CT	computerized tomography
CTA	computed tomography angiogram
CVA	cerebrovascular accident
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
EOF	end of follow-up
EoS	end of study
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	U.S. Food and Drug Administration
GBS	Guillain-Barré syndrome
GCS	Glasgow Coma Scale
GERD	gastroesophageal reflux disease
GMT	geometric mean titer
GMTR	geometric mean titer ratio
hACE2	human angiotensin-converting enzyme 2
HIV	human immunodeficiency virus
ICSR	Individual Case Safety Report
ICU	intensive care unit
ID_{50}	inhibitory dilution of 50%
Ig	immunoglobulin
IL	interleukin
IND	Investigational New Drug Application
INR	international normalized ratio
IO	intraosseous
IR	information request
ISS	integrated summary of safety
IV	intravenous

LB	lower bound
LRTI	lower respiratory tract infection
MAAE	medically attended adverse event
MCA	middle cerebral artery
MedDRA	Medical Dictionary for Regulatory Activities
MN_{50}	microneutralization assay with an inhibitory concentration of 50%
MRI	magnetic resonance imaging
mRNA	messenger RNA
NI	noninferiority
NP	nucleoprotein
NSTEMI	non-ST elevated myocardial infarction
NVX-CoV2373	Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent)
NVX-CoV2373 + NVX-CoV2515	Bivalent vaccine (Original Monovalent and Omicron BA.1)
NVX-CoV2515	Monovalent vaccine (Omicron BA.1)
NVX-CoV2540	Monovalent vaccine (Omicron BA.5)
NVX-CoV2601	Monovalent vaccine (Omicron XBB.1.5)
O/E	observed-to-expected
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	pulmonary embolism
PEA	pulseless electrical activity
PI	Principal Investigator
PIMMC	potential immune-mediated medical condition
PLWH	people living with HIV
PP-EFF	Per-Protocol Set for efficacy analysis
PP-IMM	Per-Protocol Set for immunogenicity analysis
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
PT	preferred term
PY	person-years
RBD	receptor binding domain
RNA	ribonucleic acid
RR	relative risk
rS	recombinant spike glycoprotein
RSV	respiratory syncytial virus
RT-PCR	reverse transcription-PCR
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCS	self-controlled case series
SCR	seroconversion rate
SMQ	Standard MedDRA Query
SOC	System Organ Class
SRR	seroresponse rate
SVT	supraventricular tachyarrhythmia
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UK	United Kingdom
U.S.	United States of America

USPI	United States Prescribing Information
VAERS	Vaccine Adverse Event Reporting System
VBM	variant being monitored
VE	vaccine efficacy
VOC	variant of concern

1. EXECUTIVE SUMMARY

An original Biologics License Application (BLA) has been submitted by Novavax, Inc. (the Applicant) for candidate COVID-19 vaccine, NVX-CoV2373 (proposed trade name NUVAXOVID, also referred to as NVX-CoV2373 vaccine during clinical development and to be used in this memorandum) for licensure of a single dose of NVX-CoV2373 (JN.1 strain) with a proposed indication for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status. The 2024-2025 Formula contains full-length recombinant SARS-CoV-2 spike protein based on the JN.1 strain and produced from baculovirus-infected Sf9 (fall armyworm) insect cells. It also contains Matrix-M adjuvant comprised of saponins derived from the soapbark tree (*Quillaja saponaria Molina*).

NVX-CoV2373 was authorized as Novavax COVID-19 Vaccine, Adjuvanted under Emergency Use Authorization (EUA); the Original Monovalent (Wuhan strain) was authorized on July 13, 2022, for the prevention of Coronavirus Disease 2019 (COVID-19) in individuals 18 years of age and older (2-dose series in unvaccinated individuals). Subsequent amendments leading up to the most current EUA for the 2024-2025 Formula (JN.1) are described in Section 2.5.

Data from Study 2019nCoV-301 (Study 301), which provided the basis for the EUA, also serve as the foundation for this BLA. Study 301 was a Phase 3, saline placebo-controlled, randomized (2:1), observer-blind study of a 2-dose series of the Original Monovalent vaccine in previously unvaccinated adults (Adult Main Study 301) and adolescents (Pediatric Expansion Study 301) conducted in the United States (U.S.) and Mexico. Efficacy was assessed against a clinical endpoint: polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination of the initial vaccination period (also referred to as the pre-crossover period).

Vaccine efficacy in adults, based on data from approximately 30,000 adults accrued through September 27, 2021, had a point estimate of 89.6% (95% confidence interval [CI]: 82.5, 93.8) (Section 6.1.11, Table 7). After study initiation, the protocol for Study 301 was revised to include a blinded crossover vaccination period, which was initiated on April 20, 2021. During the blinded crossover vaccination period, 15,319 (77.7%) participants who received Original Monovalent during the initial vaccination period crossed over to receive placebo (Original Monovalent to placebo) and 6,395 (64.8%) participants who had received placebo crossed over to receive Original Monovalent (placebo to Original Monovalent), with nearly 99% of participants who crossed over receiving both doses of trial vaccine. In the pre-and post-crossover period, all unsolicited adverse events (AEs) and medically attended adverse events (MAAEs) were collected through 49 days post-Dose 1, and MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune-mediated medical conditions [PIMMCs]) were collected for the duration of the study in all participants.

Pediatric Expansion Study 301 evaluated both immunogenicity and clinical efficacy of a 2-dose series of the Original Monovalent vaccine compared with saline placebo in approximately 2200 adolescents 12 through 17 years of age. Neutralizing antibody responses at Day 14 post-Dose 2 against the ancestral (Wuhan) pseudovirus in the adolescents were compared with those from adults in Adult Main Study 301, and the analyses met noninferiority (NI) criteria (i.e., pre-specified lower limits of the 95% CI for geometric mean titer ratios (GMTR) and seroresponse rates (SRR) (see Table 67 in Section 6.2.11). Vaccine efficacy against PCR-confirmed

symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination was estimated to be 79.8% (95% CI: 47.5, 92.2) (see Table 66 in Section 6.2.11).

Study 311 enrolled COVID-19 vaccine-naive adults (Part 1) and vaccine-experienced adults (Part 2) to evaluate noninferiority of a single dose of the updated BA.1 and BA.5 monovalent vaccines compared with the 2-dose series of Original monovalent (Study 301). Analyses demonstrated noninferiority of neutralizing antibody responses from a single dose of the strain updates compared with those from a 2-dose series of the Original Monovalent vaccine (Study 301; clinical efficacy population) in both populations. These data support a single dose of an updated strain.

Study 313 enrolled COVID-19 vaccine-experienced adults (Part 1) and vaccine-naive, baseline seropositive adults (part 2), respectively to evaluate the immunogenicity of a single dose of an updated monovalent vaccine (Omicron XBB.1.5). Analyses demonstrated noninferior immunogenicity in both populations. These data support the effectiveness of a single dose of NVX-CoV2373 regardless of vaccination history.

The effectiveness of a single dose of strain updates in adolescents is based on immunobridging analyses of neutralizing antibody responses in adolescents who received a booster dose in Pediatric Expansion Study 301 compared with those from previously vaccinated adults enrolled in Part 1 of Study 311. These analyses met noninferiority success criteria.

After authorization of the 2024-2025 Formula (JN.1) (August 2024) with a 2-dose regimen (i.e., 2 doses in unvaccinated individuals and 1 dose in previously vaccinated individuals), the Applicant provided the final clinical study report from Study 313 Part 2, which included immunogenicity data from vaccine-naïve individuals that supported a single-dose regimen of the 2024-2025 Formula (JN.1) in individuals 12 years of age and older. Neutralizing antibody responses induced by a single-dose regimen of the 2023-2024 Formula (Omicron XBB.1.5) in baseline seropositive vaccine-naïve adults were compared with previously vaccinated adults. Noninferiority success criteria were met for immune responses, supporting effectiveness of a single dose regardless of vaccination history (see Section 6.5.11.1).

The total safety database for NVX-CoV2373 from clinical trials includes approximately 45,000 participants who received at least one dose of vaccine. The safety analysis population in Adult Main Study 301 included participants who received at least 1 dose of Original Monovalent in the pre-crossover period (N=29,582; 19,735 Original Monovalent, 9,847 placebo; median follow-up 2.5 months post-Dose 2 based on data extraction date of August 18, 2022 or post-crossover period (N=21,714; 6,416 Original Monovalent crossover, 15,298 placebo crossover; median follow-up 8.4 months post-Dose 4 based on data extraction date of February 17, 2022). Solicited adverse reactions (ARs) were reported by a higher percentage of Original monovalent recipients than placebo recipients. Reactogenicity was reported more frequently after Dose 2 than Dose 1 and more frequently by younger adults (18 through 64 years of age) than older adults (≥65 year of age) who received Original monovalent. Severe local and systemic ARs were more frequent after Dose 2 (7.2% and 12.1%, respectively) than Dose 1 (1.2% and 2.4%, respectively). In the blinded, placebo-controlled pre-crossover period, the percentages of participants reporting unsolicited AEs, MAAEs, and SAEs were comparable between the Novavax and placebo arms. In Adult Main Study 301, there were 3 cases of myocarditis/ pericarditis reported within 14 days after Dose 2 of Original Monovalent compared with 1 case in the placebo arm. These events are included in postmarketing requirements for ongoing safety assessment.

The safety analysis population for Pediatric Expansion Study 301 included adolescents 12 through 17 years of age who received at least one dose of Original Monovalent in the pre-crossover period (N=2,232; 1487 Original Monovalent, 745 placebo) or post-crossover period (N=2,018; 665 Original Monovalent crossover, 1,353 placebo crossover). In the pre-crossover period, the median follow-up post-Dose 2 was 71 days and in the post-crossover period, the median follow-up post-Dose 4 was 30 days. Solicited ARs were reported by a higher percentage of Original Monovalent recipients than placebo recipients, and more frequently after Dose 2 (75.3% and 20.6% for solicited local ARs; 74.5% and 28.9% for solicited systemic ARs, respectively) than Dose 1 (65.5% and 28.5% for solicited local ARs; 55.2% and 40.8% for solicited systemic ARs, respectively) for Solicited local ARs. The most frequently reported severe (Grade 3) local and systemic ARs after a booster dose were injection site pain/tenderness (11.5%, respectively) and fatigue/malaise (21.4%), respectively. One serious event of myocarditis in Pediatric Expansion Study 301 was reported in an adolescent male 2 days after Dose 2. No deaths were reported during the study.

Study 311 provided safety data for updated monovalent vaccines (BA.1 and BA.5). The local and systemic reactogenicity data were consistent with the safety profile of Original monovalent. In Part 2, two related SAEs of oculomotor cranial nerve palsy were reported in close temporal relationship to the single-dose regimen of NVX-CoV2373 in COVID-19 vaccine-experienced adult participants. These events are included in product labeling and will be monitored via enhanced postmarketing pharmacovigilance. No other new safety concerns were identified.

The totality of the data summarized above and the benefit-risk assessment presented in Section 11 of this clinical memorandum support approval of a single dose of Nuvaxovid (2024-2025 Formula) (JN.1) for the indication of active immunization to prevent COVID-19 caused by SARS CoV-2 in individuals 12 years of age and older.

Across all studies submitted to this BLA, important risks that are identified with Nuvaxovid include myocarditis and/or pericarditis (important identified risk) ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves IV and VI) and vestibular neuronitis (i.e., affecting cranial nerve VIII) and atrial fibrillation and cerebrovascular accidents (CVA) (important potential risk). Myocarditis and/or pericarditis following administration of Nuvaxovid is listed in the Prescribing Information under Warnings and Precautions (5.2).

Nuvaxovid provides a recombinant protein formulation as an alternative to the available mRNA formulations for individuals who cannot take or prefer not to take a mRNA-based COVID-19 vaccine. Nuvaxovid demonstrated efficacy against virologically-confirmed COVID-19 and was associated with a substantial reduction in the risk for severe/hospitalized COVID-19 postvaccination based upon an adequately designed and well-controlled clinical efficacy endpoint study during the early phase of the pandemic when most participants were SARS-CoV-2 infection-naïve.

Pediatric studies in children <12 years of age, as required by the Pediatric Research Equity Act, were deferred for this application and will be completed after approval for use in individuals 12 years of age and older.

The Applicant also committed to conduct additional post marketing safety studies, including the assessment of pregnancy and infant outcomes following immunization during pregnancy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographic characteristics of participants in the overall safety database (integrated summary of safety (ISS) analysis included Studies 301, 311, 101, 201, 302, and 307. Study 313 was analyzed separately and was not included in the ISS safety analysis) were compared between the vaccine group and the placebo group. The percentage of participants who were 18 through 65 years of age and who were greater than 65 years of age were balanced between the two groups with approximately 15% of participants being greater than 65 years of age. The percentage of male participants (52%) was slightly higher than the percentage of female participants (48%). Distribution of racial identity across study populations was representative of the overall U.S. population, with 73% White, 17% Black, 3.5% Asian and 4% American Indian or Alaska Native. Approximately 14% of participants identified as Hispanic.

Clinical Reviewer Comment: Demographic characteristics were generally well balanced between the Original Monovalent and placebo groups for the Overall ISS Analysis set, and the safety database was generalizable to the overall U.S. population.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an ongoing global health challenge and has changed from a worldwide pandemic classification to an endemic pattern characterized by waxing and waning of attack rates over the course of a year and continued evolution of viral sub-lineages. As of February 16, 2025, SARS-CoV-2 infections has led to over 770 million cases of coronavirus disease 2019 (COVID-19), approximately 7 million deaths worldwide (WHO, 2024), and caused societal, economic, and healthcare system disruptions, which were particularly severe in 2020 and 2021.

COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines provide protection against COVID-19. COVID-19 vaccinations have been estimated to have prevented at least 14 million deaths worldwide in the first year alone after COVID-19 vaccines became available in December 2020 (Watson, et. al., 2022).

Adequately designed and well-controlled clinical efficacy endpoint trials demonstrated a high level of vaccine efficacy (approximately 90%) for the three COVID-19 vaccines that were authorized for use in the U.S., in the epidemiological setting of original Wuhan strain circulating in a SARS-CoV-2 naive population.

Due to continued SARS-CoV-2 circulation since 2020, the majority of the U.S. population over the age of 2 years has experienced at least one SARS-CoV-2 infection and is seropositive for SARS-CoV-2 nucleocapsid antibodies. As many individuals have also received at least one COVID-19 vaccine, there is a type of hybrid immunity common in the U.S. at this time with contributions from natural infection-induced immune responses and from vaccine-induced immune responses. Vaccine effectiveness in a real-world population, assessed by real-world evidence post-authorization or post-licensure, is affected by numerous factors, including genetic changes in the viral pathogen; changes in the attack rates over the years; and protective immune responses induced by either previous infections or vaccination. (Section 11, Risk Benefits Considerations and Recommendations). Ongoing vaccine effectiveness needs to be evaluated using real-world evidence as the rates of vaccination and of natural infection continue to change and as SARS-CoV-2 continues to evolve.

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. Disease symptoms vary. Many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older and individuals with certain co-morbid conditions (CDC, 2024a), may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals (CDC, 2024b). Symptoms associated with SARS-CoV-2 infection in children are similar to those in adults but are generally milder, with fever and cough most commonly reported (Irfan, et al., 2021; Liguoro, et al., 2020). However, since the January 2022 surge in cases due to Omicron BA.1, rates of COVID-19-associated hospitalizations among infants younger than 6 months old are similar to those of adults ages 65 to 74 years old (CDC, 2023). may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. In the U.S., more than 1.2 million deaths from COVID-19 have been reported to the CDC (CDC, 2024c), with a cumulative COVID-19-associated hospitalization rate of 177.3 per 100,000 people for the 2023-

2024 season, as of August 24, 2024 (CDC, 2024d). Individuals 65 years of age and older accounted for 76% of deaths (CDC, 2024e), while individuals 18 years of age and younger represent less than 0.2% of deaths (CDC, 2024e). Since the start of the pandemic, surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. COVID-19 vaccines based on the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as ancestral, reference, or original strain) were launched in the U.S, starting in December 2020. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently the Omicron variant of concern. Bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines were deployed in the U.S. starting in September 2022.

Omicron variants have continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by postvaccination (with original strain vaccines) and post-infection sera compared with pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from postvaccination and post-infection antibody responses. By spring 2023, BQ sublineages were rapidly replaced by XBB sublineages, both in the U.S. and globally. The XBB parent lineage resulted from a recombination of BA.2.10.1 and BA.2.75 sublineages, highlighting the relevance of recombination in generating new variants of concern. Recombination can occur during virus replication in cells infected by more than one variant.

Omicron XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023. By September 2024, circulating variants worldwide included XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant variant in the U.S. in September 2024 was KP.3.1.1, which was an offshoot from the KP.3 family, and was of the Omicron family. It was one of many currently co-circulating JN.1-derived variants, overtook KP.3, and continued to increase in proportion (CDC, 2024f; CDC, 2024g). As of March 2, 2025 through March 15, 2025, the dominant variants in the U.S. were Omicron LP.8.1 and XEC (CDC COVID Data Tracker: Variant Proportions).

SARS-CoV-2 evolution is complex and remains unpredictable. Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. Intrinsic viral factors, e.g., mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals. Thus far, the impressive plasticity, especially

in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1.1, XBB.1.5, or JN.1 lineage, as specified.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

2.2.1 FDA-Approved Therapies for COVID-19

Oral antivirals:

Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients (≥28 days old and weighing ≥3 kg), who are:

- Hospitalized; or
- Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Immune modulators:

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

Actemra (tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

2.2.2 Emergency Use Authorized Pharmacological Products for Pre-Exposure Prophylaxis of COVID-19, Post-Exposure Prophylaxis and/or Treatment of COVID-19

Oral antivirals:

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults and authorized for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 through 17 years of age and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death, and
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

SARS-CoV-2-targeting monoclonal antibodies:

Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them (for detail of previously authorized SARS-CoV-2-targeting monoclonal antibodies, please refer to Section 2.2.5 of the FDA Review Memorandum Dated April 18, 2023).

Immune modulators:

Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation, or ECMO.

Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

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

COVID-19 convalescent plasma:

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

2.3 Safety and Efficacy of Pharmacologically Related Products

Comirnaty and Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula)

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) is authorized for use in individuals 6 months through 11 years of age. Comirnaty and the Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) contain a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the Omicron variant KP.2 strain of SARS-CoV-2.

Spikevax and Moderna COVID-19 Vaccine (2024-2025 Formula)

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna TX Inc., is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The Moderna COVID-19 Vaccine (2024-2025 Formula) is authorized for use in individuals 6 months through 11 years of age. Spikevax and the Moderna COVID-19 Vaccine (2024-2025 Formula) contain a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the Omicron variant KP.2 strain of SARS-CoV-2.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was authorized under EUA on July 13, 2022.

Currently, Novavax COVID-19 Vaccine, Adjuvanted (2024–2025 Formula) is authorized or approved for use in multiple countries. Roughly (b) (4) million doses of the Novavax COVID-19 vaccines have been distributed worldwide and, approximately 1 million doses have been administered in the U.S. as of January 31, 2025.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

EUA 28237

- July 13, 2022: Authorization of Novavax COVID-19 Vaccine, Adjuvanted for the prevention of Coronavirus Disease 2019 (COVID-19) for individuals 18 years of age and older (2-dose series in unvaccinated individuals).
- August 19, 2022: Authorization of Novavax COVID-19 Vaccine, Adjuvanted for the prevention of Coronavirus Disease 2019 (COVID-19) for individuals 12 through 17 years of age (2-dose series in unvaccinated individuals).
- September 12, 2022: FDA reissued the August 19, 2022, letter of authorization in its entirety to revise the conditions of authorization related to Vaccine Adverse Event Reporting System (VAERS) reporting requirements for vaccination providers and Novavax, Inc. to include myocarditis and pericarditis.
- October 19, 2022: Authorization of Novavax COVID-19 Vaccine, Adjuvanted as a first booster dose (0.5 mL) to the following individuals at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine:
    - Individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and
    - Individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine.
- May 11, 2023: FDA reissued the October 19, 2022, letter of authorization in its entirety with revisions to Condition G to require the inclusion of distribution data for Novavax COVID-19 Vaccine, Adjuvanted in the monthly periodic safety reports. In addition, the product description set forth in the Scope of Authorization (Section II) was revised to reflect the previous authorization of multiple dose vials of the Novavax COVID-19 Vaccine, Adjuvanted that contain 5 doses of 0.5 mL each, as well as multiple dose vials of the Novavax COVID-19 Vaccine, Adjuvanted that contain 10 doses of 0.5 mL each.
- October 3, 2023: FDA reissued the May 11, 2023, letter of authorization in its entirety with revisions to:
    - Authorize the following uses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) to prevent COVID-19 in individuals 12 years of age and older**:**
        - A single 0.5 mL dose at least 2 months after receipt of the last previous dose of COVID-19 vaccine in individuals previously vaccinated with any COVID-19 vaccine.
        - A series of two doses (0.5 mL each) 3 weeks apart in individuals not previously vaccinated with any COVID-19 vaccine.

        - An additional dose of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) may be administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula) in individuals with certain kinds of immunocompromise. Additional doses may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.
    - Revise the conditions related to printed matter, advertising, and promotion to add additional requirements;
    - Remove the requirement that distribution of vaccines authorized under this EUA must be distributed to emergency response stakeholders as directed by the U.S. Government and make corresponding changes to the Conditions of Authorization;
    - Remove the requirement that vaccines authorized under this EUA be administered only by vaccination providers enrolled in the CDC COVID-19 Vaccination Program and make corresponding changes to the Conditions of Authorization;
    - Revise Condition G to provide flexibility to determine a different reporting interval for periodic safety reports, if appropriate;
    - No longer authorize the use of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the U.S.; and
    - Clarify the terms and conditions that relate to export of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) from the U.S.
- August 30, 2024: FDA reissued the October 3, 2023, letter of authorization in its entirety with revisions to:
    - Authorize the following uses of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) to prevent COVID-19 in individuals 12 years of age and older (in pre-filled syringes):
        - A series of two doses (0.5 mL each) 3 weeks apart in individuals never vaccinated with any COVID-19 vaccine;
        - A single 0.5 mL dose at least 3 weeks after the previous dose of Novavax COVID-19 Vaccine, Adjuvanted to complete the 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted in individuals vaccinated only with one dose of any Novavax COVID-19 Vaccine, Adjuvanted;
        - A single 0.5 mL dose at least 2 months after receipt of the last previous dose of COVID-19 vaccine in individuals vaccinated with any COVID-19 vaccine, other than Novavax COVID-19 Vaccine, Adjuvanted, or with two or more doses of Novavax COVID-19 Vaccine, Adjuvanted;
        - An additional dose may be administered at least 2 months following the last dose of a COVID-19 vaccine (2024-2025 Formula) in individuals with certain kinds of immunocompromise. Additional doses may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.
    - No longer authorize Novavax COVID-19 Vaccine, Adjuvated (Original Monovalent) for export from the U.S.

- No longer authorize the use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula).
- Add new Condition O to require a post-authorization study to evaluate immune responses after receipt of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula.
- Revise Condition J to add a requirement to submit a real-time monthly stability (relative potency) data and other requirements related to product stability.

Major pre-submission BLA-associated regulatory activity:

- June 10, 2021: Agreed Initial Pediatric Study Plan.
- December 6, 2021: Pre-EUA Meeting, Introduction Serum Institute of India as a new manufacturing facility.
- October 4, 2022: FDA responds to Novavax "Pre-Pre BLA" questions.
- March 3, 2023: Teleconference to discuss expectations for the clinical aspects of the BLA submission.
- April 14, 2023: Type B, Pre-BLA Meeting (Written Responses Only), FDA comments were received by Novavax.
- July 6, 2023: Novavax submits Roll 1 of BLA (b) (4) for FDA review; Teleconference to align on the pediatric development program for Novavax's COVID-19 Vaccine.
- July 30, 2023: Novavax submits Roll 2 of BLA (b) (4) for FDA review.
- August 16, 2023: Novavax submits Roll 3 of BLA (b) (4) for FDA review.
- August 18, 2023: Teleconference to discuss deficiencies with the Novavax COVID-19 Vaccine BLA which included the size and organization of the documents in the BLA and several concerns involving the datasets. FDA recommended that Novavax (b) (4)
- August 22, 2023: Novavax (b) (4)
- September-December 2023: Multiple Written Responses sent to Novavax regarding a BLA resubmission.
- December 21, 2023: Teleconference to discuss the volume and content of the Novavax COVID-19 vaccine BLA re-submission. The Agency requested granular details on the BLA submission, which had a page count of 17.4 million pages. A follow-up Clinical Applicant Communication was sent to Novavax on December 22, 2023.
- January 2, 2024: Novavax response to December 22, 2023, communication where Novavax agreed to the recommended changes to the FAEF (Findings About Events or Interventions) dataset for Study 301, removing the audit trails, case report forms, and line listings from the BLA submission, and submitting a revised table of contents.
- January 8-9, 2024: Written Responses and Teleconference regarding the Integrated Summary of Safety Statistical Analysis Plan (ISS SAP).
- January 25, 2024: Comments were sent to Novavax regarding the BLA resubmission.
- January 31, 2024: Roll 1 of BLA 125817 was submitted.
- February 27, 2024: Response to February 20, 2024, requested information on clinical

diagnostic assays for Section 5.3.1 was provided.

- February 29, 2024: Roll 2 of BLA 125817 was submitted.
- March 6, 2024: Response to chemistry, manufacturing, and controls (CMC) information request (IR) requesting the regulatory inspection history on 3 of Novavax's manufacturing facilities.
- April 1, 2024: Roll 3 of BLA 125817 was submitted.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Certain Applicant responsibilities were transferred from Novavax Inc. to PPD, Inc. for the conduct of clinical study 2019-nCoV-101 Part 2; in addition, certain responsibilities were transferred from Novavax Inc. to Syneos Health UK Limited for the conduct of clinical study 2019nCoV-307 (see Section 5.3 for Table of Studies). All clinical studies that were included in this BLA were in compliance with Good Clinical Practice as per 21 CFR 312.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Studies 301, 311, 313, 101, 501, 302, and 307
Was a list of clinical investigators provided? [x] Yes ☐ No (Request list from Applicant)
Total number of investigators identified: 3653
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study: Is an attachment provided with details of the disclosable financial interests/arrangements? [x] Yes ☐ No (Request details from Applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes [OBJ] No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2 Is an attachment provided with the reason? [x] Yes ☐ No (Request explanation from Applicant)

Reviewer Comment: There was 1 investigator in Study 302 who had a partner who owned (b) (4) *shares of Novavax stock. A second Investigator in Study 302 had a Spouse who was developing* (b) (4)

provided by the Applicant. Given that Study 302 is only a supportive safety study, there is minimal chance that these disclosures will have a substantive impact on the integrity of this review. Further, it is unlikely that these financial arrangements affected the outcome of the study.

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

4.1 Chemistry, Manufacturing, and Controls

The CBER CMC reviewer identified no issues that would impact the conclusions of the clinical review.

4.2 Assay Validation

Two clinical diagnostic and immunogenicity assays were used to assess serostatus (to indicate recent or prior infection with SARS CoV-2) and clinical endpoints in pre-licensure clinical trials. The Abbott RealTi*me* SARS CoV-2 assay is a commercially available RT-PCR kit that was authorized by FDA under Emergency Use. The assay's performance was verified in a validation study performed at the (b) (4) . Roche Elecsys anti-SARS CoV-2 N antibody assay is an immunoassay for the detection of antibodies to SARS CoV-2 in human serum or plasma to help identify individuals with recent or prior infection to SARS CoV-2. The assay's performance was verified in a validation study performed at the (b) (4) . Both the assays were adequately validated and found to be suitable for their intended purpose.

To assess the immune response postvaccination, the Applicant used two immunoassays: a wild-type virus microneutralization assay and a pseudotype virus neutralization assay. Both were adequately validated and deemed suitable for their intended purpose during the EUA reviews for the Novavax COVID-19 vaccine.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Toxicology Reviewer Memorandum. No significant toxicology signal was identified.

4.4 Statistical

No major statistical issues were identified by CBER statistical reviewers in this application. The key statistical analyses for safety and efficacy were confirmed by CBER statistical reviewers.

4.5 Pharmacovigilance

Novavax is conducting safety-related post-authorization studies for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Novavax has a pharmacovigilance plan (Version 2.3, dated September 4, 2023) to monitor safety concerns that could be associated with the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). The plan includes the following:

- Important Identified Risks: anaphylaxis, myocarditis and/or pericarditis.
- Important Potential Risks: Ocular motor cranial nerve disorders (i.e., affecting cranial nerves III, IV, or VI), cranial nerve VIII disorders, supraventricular tachycardia, Cerebral Vascular Accident.
- Missing information: use in pregnancy and while breastfeeding; use in immunocompromised patients; use in frail patients with comorbidities (e.g., chronic

obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders); use in patients with autoimmune or inflammatory disorders; interaction with other vaccines; and long-term safety.

Given the concerns outlined in this memorandum regarding the two clinical trial cases of ocular motor cranial nerve palsies and one case of vestibular neuronitis involving the vestibulocochlear cranial nerve VIII from Study 2019nCoV-311, FDA requested that Novavax add "Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)" and Cranial nerve VIII disorders (including vestibular neuronitis) as Important Potential Risks in the pharmacovigilance plan.

In addition, given the lack of a safety signal to date for "Vaccine-associated enhanced disease (VAED, including vaccine-associated enhanced respiratory disease (VAERD)," and the initial inclusion of this safety concern on a theoretical basis, FDA requested that Novavax remove this safety concern as an Important Potential Risk from the PVP.

Applicant Pharmacovigilance Activities

The Applicant will conduct both passive and active surveillance to monitor postmarketingsafety for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Please refer to Section 11.6 (Recommendations on Postmarketing Actions) and the (b) (6) review memorandum for a description of planned pharmacovigilance activities.

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

5.1 Review Strategy

Efficacy Analysis in Previously Unvaccinated Adults and Adolescents for the Original Monovalent (Wuhan formula) Vaccine

The efficacy data supporting a 2-dose series of the Original Monovalent vaccine in previously unvaccinated adults ≥18 years of age, was assessed from the Adult Main Study 301 and the immunogenicity and descriptive efficacy analyses supporting a 2-dose series of the Original Monovalent vaccine in previously unvaccinated adolescents 12 through 17 years of age from Pediatric Expansion Study 301. Effectiveness of the 2023-2024 Formula (XBB.1.5) in adults and adolescents was supported by the immunogenicity data from modified Novavax COVID-19 Vaccine, Adjuvanted formulations [monovalent vaccine (Omicron BA.1) and monovalent vaccine (Omicron BA.5)] against the Omicron BA.1 and BA.5 sublineages in adults (Study 311 Parts 1 and 2), and by the nonclinical and CMC data supporting the XBB.1.5 strain update. Specifically, an immune bridge was established between the Omicron subvariant monovalent vaccines and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), indicating similar effectiveness of the monovalent vaccines compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

Primary Safety Analysis for the Original Monovalent (Wuhan) Vaccine

Adult Main and Pediatric Expansion Study 301 is the primary basis for the safety analysis of the BLA. The total safety database is N=31,735, and contains:

- 17 months of safety follow-up post-2nd dose for adults 18 years and older, including 6 months of safety follow-up after the third dose for adults (n=29,582), (Adult Main Study 301, Conduct Period – December 27, 2020, through August 18, 2022).
- 12 months of follow-up post-2nd dose for adolescents 12 through 17 years of age ,

including a median duration of at least 3-month safety follow-up and 6 months of unrestricted safety follow-up after the third dose for adolescents (n=2,153), (Pediatric Expansion Study 301 12-Month Adolescent Report, Conduct Period December 27, 2020, to August 6, 2022).

Safety follow-up include solicited local adverse events (AEs) for 7 days, solicited systemic AEs for 7 days, unsolicited AEs, Medically Attended Adverse Events, Serious Adverse Events (SAEs) for the entire duration of safety follow-up, Adverse Events of Special Interest (AESIs), and Adverse Events leading to study discontinuation. All safety data previously reviewed to support a prior EUA authorization have been verified using the submitted datasets. The safety analyses from the datasets submitted on January 24, 2025, are included in this BLA review.

Safety Analysis to Support an Updated Vaccine Technology 2023-2024 Formulation and 2024-2025 Formula)

The safety data from the Final Clinical Study Report for Clinical Study 2019nCoV-311 Part 1 and the Final Clinical Study Report for Clinical Study 2019nCoV-311 Part 2 are used to support the safety of an updated Novavax COVID-19 vaccine.

Immunogenicity and Safety Analysis to Support a Single Dose of the Updated Novavax Vaccine Regardless of Vaccine History

Effectiveness of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals 18 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:

- Immunogenicity of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in COVID-19 vaccine-naïve individuals 18 years of age and older who have evidence of prior COVID-19 natural infection compared with previously COVID-19 vaccinated individuals 18 years of age and older (Study 313 Part 2)

Safety of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals 18 years of age and older, irrespective of prior COVID-19 vaccination status, is based on:

- Safety of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in COVID-19 vaccine-naïve individuals 18 years of age and older who have evidence of prior SARS-CoV-2 natural infection (Study 313 Part 2)
- Safety of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in COVID-19 vaccine-experienced individuals 18 years of age and older (Study 313 Part 1)

Supportive Pooled Safety Analysis

The following studies with the approximate sample sizes below:

- Study 101, n=500
- Adult Main Study 301, n=30,000 adults
- Pediatric Expansion Study 301, 2,000 adolescents
- Study 302, n=7,600
- Study 307, n=900 (n=7 for the primary series)
- Study 501, n=2,200

- Study 311, Part 1, n=270
- Study 311, Part 2 (excluding the 6-month data), n=250

The pooled Safety Analysis will include vaccine safety analyses as discussed above except for solicited adverse events which were not collected in some of the studies (i.e., Study 307).

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

The primary source of data considered for review of this investigational vaccine were documents submitted to STN 125817/0. The following sections were reviewed in support of this application:

Module 1, all sections: Administrative Information and Prescribing Information

Section 2.2 Introduction

Section 2.5 Clinical Overview

Section 2.7.3 Summary of Clinical Efficacy

Section 2.7.4 Summary of Clinical Safety

Section 2.7.6 Synopses of Individual Studies

Section 5.2 Tabular Listing of All Clinical Studies

Section 5.3.5.1 Clinical Study Reports

During the BLA review period, the Applicant submitted a total of 100 amendments. Only amendments relevant to the clinical review are included in the table below.

Table 1. Selected Amendments to the Submission

Amendment Number	Date Received	Description
0	01/31/24	Rolling BLA – Original Submission Part 1 of 3 containing clinical data for studies 2019nCoV-101 Part 1, 2019nCoV-101 Part 2, and 2019nCoV-307
2	02/29/24	Rolling BLA – Original Submission Part 2 of 3 containing clinical data for studies 2019nCoV-501, 2019nCoV-302, and 2019nCoV-311 Part 2, request for deferral of pediatric studies, and copy of Agreed initial Pediatric Study Plan (iPSP)
4	04/01/24	Rolling BLA – Original Submission Part 3 of 3 containing draft labeling
7	04/10/24	Response to information request (IR) regarding proposed U.S. Prescribing Information (USPI) draft labeling
8	04/12/24	Follow-up response to IR regarding USPI draft labeling
9	04/16/24	Response to IR regarding PREA waiver request
12	04/26/24	Response to IR regarding the Integrated Summary of Safety report (ISS)
14	04/29/24	Response to IR regarding ISS datasets
15	04/29/24	Clinical Study Report and datasets for study 2019nCoV-311 Part 2
17	05/04/24	Response to IR regarding coding dictionaries for each study in BLA 125817 and the ISS
20	05/14/24	Response to CBER advice regarding updated datasets for clinical studies 2019nCoV-101, 2019nCoV-302, and 2019nCoV-501
25	06/11/24	Request for CBER advice regarding Day 120 (4-month) Safety Update for clinical studies 2019nCoV-101 Part 2, 2019nCoV-301 (Adults), and 2019nCoV-301 (Pediatric Expansion)
27	07/15/24	Response to IR regarding study 2019nCoV-313 study report

Amendment Number	Date Received	Description
29	07/29/24	Response to IR regarding Day 120 (4-month) Safety Update
30	07/29/24	Response to IR regarding PREA waiver request
31	08/05/24	Response to IR (submitted under IND 22430) regarding revisions to the Pediatric Study Plan
32	08/23/24	Response to IR regarding updated draft USPI labeling
33	08/29/24	Response to IR regarding study 2019nCoV-301 Adult Addendum and ISS datasets
34	08/29/24	Response to IR regarding Day 120 (4-month) Safety Update for studies 2019nCoV-101 Part 2 and 2019nCoV-301 clinical study report (CSR) for study 2019nCoV-311 Part 1
36	09/13/24	Response to IR regarding submission of final CSRs, study report addenda, and updated datasets
39	10/02/24	Response to IR regarding final CSR for study 2019nCoV-101 Part 2
40	10/04/24	Response to the mid-cycle meeting communication
41	10/25/24	Response to IR regarding PREA waiver request
45	11/15/24	Response to IR regarding study 2019nCoV-313 Part 2 final CSR; updated draft labeling
47	11/27/24	Response to IR regarding deferred pediatric studies
48	12/04/24	Response to IR regarding study 2019nCoV-313 Part 1 datasets
50	12/11/24	Response to IR regarding study 2019nCoV-313 Part 1 datasets
54	12/17/24	Meeting minutes from CBER-Novavax 12/06/24 teleconference regarding clinical datasets
56	12/20/24	Meeting minutes from CBER-Novavax 12/17/24 Late Cycle Meeting; response to IR regarding clinical datasets
57	12/23/24	Response to IR regarding clinical datasets for study 2019nCoV-301 (Adults)
58	12/30/24	Response to IR regarding clinical datasets for studies 2019nCoV-301 (Adults) and 2019nCoV-301 (Pediatric Expansion)
62	01/09/25	Response to IR regarding clinical datasets for studies 2019nCoV-101 (Part 1 and Part 2), 2019nCoV-501, 2019nCoV-302, and 2019nCoV-311 (Part 1 and Part 2)
64	01/24/25	Response to IR regarding updated tables, CSR addenda, and updated draft USPI labeling
66	01/29/25	Response to IR (submitted under IND 22430) regarding PREA deferral request
79	02/27/25	Response to IR regarding narratives for studies 301 and 311
87	03/10/25	Response to IR regarding postmarketing safety database to address atrial fibrillation
95	03/18/25	Novavax's response to IR regarding USPI draft labeling
96	03/18/25	Novavax's response to IR regarding acknowledgement of Postmarketing Activities
98	03/19/25	Novavax's response to IR regarding postmarketing activities.
99	03/21/25	Novavax's response to IR regarding cardiac arrest cases
101	03/24/25	Novavax's response to IRs regarding total number of investigators and cardiomyopathy/cardiac failure
104	03/27/25	Novavax's response to IR regarding revised draft USPI labeling
105	03/27/25	Novavax's response to IR regarding single dose data in baseline seronegative individuals
106	03/28/25	Novavax's response to IR regarding bivalent vaccine data
107	03/31/25	Novavax's response to IR regarding revised draft USPI labeling

Source: Reviewer table

5.3 Table of Studies/Clinical Trials

Table 2. Overview of Clinical Studies

Study Number/ Country	Description	Approximate Number of Participants	Studied Primary Series (PS) and/or Booster (B)	Study Status
Study 301 Adult Main USA, Mexico	Phase 3, randomized, observer-blinded, placebo-controlled to safety, efficacy, immunogenicity in adults ≥18 years of age with booster	30,000	Primary series and monovalent booster (PS, B)	Complete
Study 301 Pediatric Expansion	Phase 3, randomized, observer-blinded, placebo-controlled to safety, efficacy, immunogenicity adolescents 12 through 17years of age with booster	2,000	Primary series and monovalent booster (PS, B)	Complete
Study 307 Adult USA	Phase 3, Randomized, Observer-Blinded, Study to Compare the Immunogenicity and Safety of 3 Lots of Original Monovalent in Adults (primary series NVX (n=7), Pfizer, Moderna, Janssen)	900	Monovalent booster Supportive safety (B) (NVX PS, B n=7)	Complete
Study 311 Part 2 BA.5 Prototype Bivalent BA.5	Phase 3, randomized, observer-blinded study to evaluate the safety and immunogenicity of Novavax SARS-CoV-2 BA.1 and BA.5 booster vaccine formulations, administered as either monovalent or bivalent vaccine [combination of Omicron BA.5 with the ancestral strain (Wuhan-Hu-1)], in adults 18through 64 years of age previously immunized with mRNA COVID-19 monovalent prototype vaccines (Moderna and/or Pfizer)	764	Monovalent and Bivalent boosters (B)	Complete
Study 311 Part 1 BA.1, prototype, bivalent BA.1 Australia	Phase 3, randomized, observer-blinded study to evaluate the safety and immunogenicity of Novavax SARS-CoV-2 BA.1 and BA.5 booster vaccine formulations, administered as either monovalent components or combined with the original strain (Wuhan-Hu-1), in adults 18 through64 years of age previously immunized with mRNA COVID-19 monovalent prototype vaccines (Moderna and/or Pfizer)	951	Monovalent and Bivalent boosters (B)	Complete
Study 313 Part 2, XBB.1.5 U.S.	Phase 2/3 open label study in vaccine-naive adults 18 years and older	330	Monovalent single dose	Complete
Study 302 United Kingdom	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study in adults 18 through 84 years of age	7,600	Supportive safety (PS, B)	Complete
Study 501 South Africa	Phase 2, randomized, observer-blinded, placebo-controlled study in healthy HIV-negative adults 18 through 84 years of age and HIV-positive adults 18 through 64 years of age	2,200	Supportive safety (PS)	Complete

Study Number/ Country	Description	Approximate Number of Participants	Studied Primary Series (PS) and/or Booster (B)	Study Status
Study 101, Part 1 Australia	Phase 1, randomized, observer-blinded, placebo-controlled in adults 18 through59 years of age	30	Supportive safety (PS)	Complete
Study 101, Part 2 Australia/USA	Phase 2, randomized, observer-blinded, placebo-controlled in adults 18 through84 years of age	500	Supportive safety (PS, B)	Complete

Source: Reviewer table
Abbreviations: PS= primary series; B=booster; NVX=Novavax

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Adult Main Study 301

NCT04611802

Title: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1 Adjuvant in Adult Participants ≥18 Years With a Pediatric Expansion in Adolescents (12 to <18 Years)

6.1.1 Objectives

Primary Objective

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic coronavirus disease 2019 (COVID-19) illness diagnosed ≥7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥18 years of age.

Key Secondary Objective

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed symptomatic COVID-19 illness due to a SARS-CoV-2 variant not considered as a “variant of concern / interest” according to the CDC Variants Classification, diagnosed ≥7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥18 years of age.

Other Secondary Objectives

- To evaluate the efficacy of a 2-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M1 compared to placebo against PCR-confirmed moderate-to-severely symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination in the initial set of vaccinations of adult participants ≥18 years of age.
- To assess vaccine efficacy (VE) against ANY symptomatic SARS-CoV-2 infection.
- To assess VE according to race and ethnicity.

6.1.2 Design Overview

Adult Main Study 301 is a randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of Original Monovalent in adults ≥18 years of age. The study was conducted at 119 sites in the U.S. and Mexico. Study 301 also included an adolescent primary series expansion substudy (Pediatric Expansion substudy) and a booster dose substudy. The Adult Main Study was initiated on December 27, 2020 (first participant screened) and completed enrollment on February 18, 2021. Participants were followed for up to 24 months after the second dose for safety and efficacy assessments through the end of the study on August 18, 2022.

The Adult Main Study consisted of a screening period up to 30 days prior to Day 0; initial vaccination series (Days 0 and 21 + 7 days); crossover vaccination series with the second injection administered 21 + 7 days after the first in the series; outpatient study visits on Days 0, 21 (+ 7 days), and 35 (+ 7 days) in the initial set of vaccinations; and safety follow-up calls 3 and 6 months post-crossover.

Study vaccination regimens comprised an initial series of 2 intramuscular (IM) injections of Original Monovalent or placebo (0.9% normal saline), administered 21 days apart on Day 0 and Day 21 (+ 7 days), ideally in alternating deltoids. For blinding purposes, all participants were vaccinated using the same injection volume (0.5 mL). All vaccinations were administered on an outpatient basis by qualified vaccine administrators in a way to maintain the blind as described in the Pharmacy Manual. Seven-day reactogenicity was collected via eDiary following each dose during the initial vaccination series. Unsolicited treatment-emergent adverse events (TEAEs) and medically attended adverse events (MAAEs) were collected through 28 days following the second vaccination and vaccine-related MAAEs, adverse events of special interest (AESIs), and SAEs will be collected through the end of the study.

A total of 29,945 adult participants were randomized 2:1 to receive 2 intramuscular injections (Dose 1 and Dose 2) of either Original Monovalent or saline placebo. Participants were stratified by age group (18 through to 64 years of age and ≥65 years of age, with target enrollment of 25% of participants in the older age strata). Priority enrollment was given to those at high risk for COVID-19 by virtue of Black/African American or Native American race, Hispanic or Latino ethnicity, co-morbid conditions (e.g., obesity [BMI >30 kg/m^2], chronic kidney or lung disease, cardiovascular disease, or diabetes mellitus type 2), and life circumstances (living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances [e.g., factory or meat packing plants, essential retail workers]). Individuals with clinically stable chronic conditions who had no previous history of laboratory-confirmed SARS-CoV-2 infection or COVID-19 prior to randomization were eligible. The study excluded individuals with immunodeficiencies (those with well-controlled HIV infection were excepted), those who received immunosuppressive therapy, or immunoglobulin or blood derived products within 90 days, were pregnant or breastfeeding.

In response to evolving public health recommendations for and availability of COVID-19 vaccines authorized for Emergency Use Authorization (EUA), the Applicant modified the study plan after the EUA-required safety data were accrued (median duration of 2 months safety follow-up after the second vaccination) to offer crossover from the originally-assigned study treatment (vaccine or placebo) to the other study treatment in a blinded fashion (Dose 3 and Dose 4 “blinded crossover”).

Efficacy was assessed through daily surveillance of symptoms suggestive of COVID-19 throughout the study follow-up. Symptoms of COVID-19 experienced by participants during postvaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab. Additionally, participants were given an at-home test to use for 3 days (3-Day Self-Collection Kit). For the diagnosis of SARS-CoV-2 infection, FDA-authorized PCR tests were used, irrespective of whether the test was performed by participant with 3-Day Self-Collection Kit or at study sites, and swabs were sent to a central laboratory. Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay) by the central laboratory was required to meet the primary and secondary efficacy endpoint case definitions.

The primary efficacy endpoint was assessed with data collected up to the blinded crossover period (median 2 months after Dose 2, April 2021). Participants who were unblinded with an intention to receive a COVID-19 vaccine under EUA were censored past the time of unblinding. One protocol-specified primary efficacy analysis for this study was conducted using all pre-crossover blinded follow-up data.

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

Following collection of sufficient safety data from the initial series of injections to support application for EUA, participants were scheduled for administration of an additional series of 2 IM injections of the alternate study material 21 days apart ("blinded crossover", with initial placebo recipients receiving Original Monovalent and initial Original Monovalent recipients receiving placebo using the same procedure followed for the initial set of vaccinations to ensure that the integrity of blinding). Unsolicited TEAEs and MAAEs were collected through 28 days following the second vaccination and vaccine-related MAAEs, AESIs, and SAEs were collected through the end of the study (August 18, 2022).

Adult participants who remained in study follow-up (blinded or unblinded) and met eligibility criteria were offered a booster injection of Original Monovalent no less than 6 months after completion of active vaccination (initial or crossover) as part of a Booster Amendment. Prior to the booster vaccine dose, a nasal swab and blood sample were obtained to determine the study participants' current serologic and virologic status. Seven-day reactogenicity was collected via eDiary as performed after the earliest 2 doses of study drug during the initial vaccination period. Similarly, unsolicited TEAEs and MAAEs were collected through 28 days following the booster dose and vaccine-related MAAEs, AESIs, and SAEs were collected through the end of the study (August 18, 2022).

6.1.3 Population

The study enrolled nonpregnant, non-lactating individuals ≥18 years of age at screening who, by virtue of age, race, ethnicity, or life circumstances, are considered at substantial risk of exposure to and infection with SARS-CoV-2 and were willing and able to give informed consent prior to study enrollment and to comply with study procedures, were medically stable, who agreed not to participate in any other SARS-CoV-2 prevention or treatment trials for the duration of the study. Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile [i.e., hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months]) agreed to be heterosexually inactive from at least 28 days prior to enrollment and through 3 months after the last vaccination OR agree to consistently use a medically acceptable method of contraception from at least 28 days prior to enrollment and through 3 months after the last vaccination.

- For the Booster Amendment only, active participants who received a full dose regimen of active vaccine (SARS-CoV-2 rS with Matrix-M1 adjuvant) or any authorized/approved COVID-19 vaccine were eligible for participation. Such participants were required to demonstrate receipt by producing valid documentation of vaccination at the booster visit.

Pertinent exclusion criteria included:

- Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy.
- Chronic administration (defined as >14 continuous days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days prior to study vaccination.

Site-Specific Sub-Study[1]

Inclusion Criteria

To be included in the sub-study, participants were required to meet all the following criteria to be enrolled in this study:

- Be an active, enrolled participant in the 2019nCoV-301 study.
- Adults 18 years of age or older or adolescents 12 to <18 years of age at initial screening for the parent study.
- Willing and able to give informed consent and assent prior to substudy enrollment and to comply with extra study procedures.
- Documented receipt of the 2 doses of the primary series of Original Monovalent and the booster (third dose) of Original Monovalent in the parent protocol. The booster dose must have been administered at least 6 months prior to entering the substudy.
- Participants of childbearing potential (defined as any participant who has experienced menarche and who is NOT surgically sterile or postmenopausal) must agree to be heterosexually inactive from at least 28 days prior to entering and through the end of the substudy OR agree to consistently use a medically acceptable method of contraception for the 28 days of follow-up for the substudy.
- Is medically stable, as determined by the investigator (based on review of health status, vital signs (to include body temperature) and targeted physical examination (if medically indicated by reported symptoms). Vital signs must be within medically acceptable ranges prior to administration of study vaccination.
- Agree to not participate in any other non-Original Monovalent study during the substudy.
- Note: For participants who develop COVID-19, anti-SARS-CoV-2 therapy (approved, authorized, or investigational) was permitted.

Exclusion Criteria

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

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

  Note: Well-controlled human immunodeficiency virus [HIV] with undetectable HIV RNA [<50 copies/mL] and CD4 count >200 cells/µL for at least 1 year, documented within the last 6 months, is NOT considered an unstable chronic illness. Participant's or parent's/caregiver's verbal report will suffice as documentation.

- Participation in research involving an investigational product (drug/biologic/device)

1. In an analysis of a subset of participants receiving a booster dose, 2 cohorts of participants likely to meet per-protocol criteria were selected randomly from 7 reliably productive sites whose participants were included in the substudy to collect Day 35 blood samples during the blinded crossover vaccination period.

administered within 45 days prior to first study vaccination.

- History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19. A previous diagnosis of COVID-19 during participation in this trial was not exclusionary for the Booster Amendment.
- Received any vaccine within 4 days prior to first study vaccination or planned receipt of any vaccine before Day 49 (i.e., 28 days after second vaccination), except for influenza vaccination, which may be received ≥4 days prior to or ≥7 days after either study vaccination. Rabies vaccine, at any time it is medically indicated, was not exclusionary. Prior receipt of another approved or authorized COVID-19 vaccine prior to booster injection was not exclusionary in the Booster Amendment. Such participants were required to provide documentation of vaccine and date(s) of administration.
- Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression. NOTE: Stable endocrine disorders (e.g., thyroiditis, pancreatitis, including stable diabetes mellitus) were NOT excluded.
- Chronic administration (defined as >14 continuous days) of immunosuppressant or systemic glucocorticoids causing clinically significant immunocompromise (i.e., ≥20 mg of prednisone per day or equivalent), within 90 days prior to first study vaccination and/or third (booster) vaccination.
- Received immunoglobulin or blood-derived products, within 90 days prior to first study vaccination and/or third (booster) vaccination.
- Active cancer (malignancy) on chemotherapy that is judged to cause clinically significant immunocompromise within 1 year prior to first study vaccination (with the exception of malignancy cured via excision, at the discretion of the investigator). This criterion was not applicable to participants diagnosed during participation in this trial who went on to participate in the Booster Amendment.
- Any known allergies to products contained in the investigational product.
- Women who were breastfeeding, pregnant, or who planned to become pregnant within 3 months following last study vaccination.
- Any other condition that, in the opinion of the investigator, would pose a health risk to the participant if enrolled or could interfere with evaluation of the trial vaccine or interpretation of study results.
- Study team member or first-degree relative of any study team member (inclusive of Applicant, and study site personnel involved in the study).
- Current participation in any other COVID-19 prevention clinical trial.
- Adult participants who had not received a full dose of any authorized/approved COVID-19 vaccine and were unable to provide valid documentation of vaccination were excluded from the Booster Amendment.

Adult and adolescent participants meeting any of the following criteria were to be excluded from the substudy:

- History of laboratory-confirmed (by PCR or other antigen testing) COVID-19 infection ≤4 months prior to entering the substudy.
- Known to be clinically significantly immunocompromised.

- Received immunoglobulin, blood-derived products, or immunosuppressant drugs within 90 days prior to entering substudy.
- Women who were breastfeeding, pregnant, or who planned to become pregnant prior to the end of substudy.
- History of confirmed myocarditis and/or pericarditis since enrollment to the parent study.
- Any condition that, in the opinion of the investigator, might pose a health risk to the participant, interfere with protocol compliance, or interfere with evaluation of the trial vaccine.
- Study team member or immediate family member of any study team member (inclusive of Applicant, clinical research organization [CRO], and study site personnel involved in the conduct or planning of the substudy).

6.1.4 Study Treatments or Agents Mandated by the Protocol

The Novavax Prototype vaccine is a SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (based on Wuhan-Hu-1 isolate). The SARS-CoV-2 rS vaccine is administered with Matrix-MTM adjuvant (previously referred to as Matrix M1), a saponin-based adjuvant developed at Novavax AB (Uppsala, Sweden) and derived from fractionated *Quillaja* saponins, phosphatidylcholine, and cholesterol.

Placebo was sterile normal saline (0.9% sodium chloride in water).

6.1.5 Directions for Use

Two intramuscular injections (Dose 1 and Dose 2) of either Original Monovalent (containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) or saline placebo were administered 21 days apart, at Day 0 and Day 21 (vaccination window of up to +7 days).

In the **Booster Amendment**, all participants who provided informed consent for this segment of the study received an open-label single dose of active vaccine (SARS-CoV-rS adjuvanted with 50 µg Matrix-M1). Adult participants received the booster dose no less than 6 months after completion of their active vaccination (initial or crossover series) and adolescent participants received the booster dose no less than 5 months after completion of the active vaccination (initial or crossover series).

6.1.6 Sites and Centers

Participants were enrolled from 119 clinical sites in the U.S. and Mexico.

6.1.7 Surveillance/Monitoring

Efficacy

The case definition used for COVID-19 is as follows:

Mild COVID-19 (≥1 of the following):

- Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
- New onset cough

- ≥2 additional COVID-19 symptoms:
    - New onset or worsening of shortness of breath or difficulty breathing compared to baseline
    - New onset fatigue
    - New onset generalized muscle or body aches
    - New onset headache
    - New loss of taste or smell
    - Acute onset of sore throat, congestion, or runny nose
    - New onset nausea, vomiting or diarrhea

OR Moderate COVID-19 (≥1 of the following):

- High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days)
- Any evidence of significant lower respiratory tract infection (LRTI):
    - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline)
    - Tachypnea: 24 to 29 breaths per minute at rest
    - SpO_2: 94% to 95% on room air
    - Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or LRTI
- Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor).

OR Severe COVID-19 (≥1 of the following):

- Tachypnea: ≥30 breaths per minute at rest
- Resting heart rate ≥125 beats per minute
- SpO_2: ≤93% on room air or PaO_2/FiO_2 <300 mmHg
- High flow oxygen (O_2) therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure)
- Mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following:
    - Acute respiratory failure, including acute respiratory distress syndrome
    - Acute renal failure
    - Acute hepatic failure
    - Acute right or left heart failure
    - Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg)

  - Acute stroke (ischemic or hemorrhagic)
  - Acute thrombotic event: acute myocardial infarction, deep vein thrombosis (DVT), pulmonary embolism (PE)
  - Requirement for: vasopressors, systemic corticosteroids, or hemodialysis
- Admission to an intensive care unit (ICU)
- Death

Adult participants in the Adult Main Study and Booster Amendment were provided with a thermometer and instructed to monitor their body temperature daily throughout the study and to record body temperature and any other relevant symptoms daily in their eDiary. Those who did not complete their daily eDiary entries and did not report temperature and symptoms for ≥7 days were contacted by phone to assess clinical status and maintain engagement in the study.

When fever or other specified symptoms were reported in the eDiary for at least 2 consecutive days for the same symptom, participants were directed via the eDiary to begin daily nasal self-swabbing for PCR testing at home for a total of 3 days and to initiate daily completion of the FLU-PRO symptom reporting instrument for 10 days after COVID-19 symptom onset or until the participant experienced 2 consecutive asymptomatic days.

In addition, the eDiary alerted the study site to contact the participant to schedule an in-person Acute Illness Visit. During the first 4 days after the second vaccination or third (booster) vaccine dose in the Booster Amendment when solicited systemic reactogenicity symptoms could have been similar to those of COVID-19, investigators used their clinical judgement to decide if an Acute Illness visit was warranted. Active surveillance for COVID-19 was continued after the blinded crossover through the end of the study. For participants in the Booster Amendment, active surveillance was continued through the second 12 months of the study following the booster. After the first day of home nasal swabbing, repeat nasal self-swabs were obtained daily for a total of 3 days to ensure capture of intermittent shedding.

Safety

Safety assessments were collected via the eDiary after the initial set of vaccinations and included participant-recorded solicited (local and systemic reactogenicity) events through 7 days following each injection in the; unsolicited AEs and MAAEs were collected through 49 days, i.e., 28 days after second injection of the initial and crossover series.

MAAEs attributed to vaccine, AESIs, SAEs and investigator-assessed targeted physical examination findings, including vital sign measurements, were collected at specified time points. Safety follow-up phone calls were conducted at 3 and 6 months (±30 days) post-crossover to collect MAAEs attributed to vaccine, AESIs, and SAEs in all participants who received crossover vaccinations. Follow-up was continued via remote contacts through study completion. During the second 12 months of follow-up after the initial set of vaccinations, participants were queried at specified timepoints, approximately every 3 months via remote contacts through study completion (except when a visit was scheduled and replaced the remote contact) or at scheduled visits (i.e., Month and 24) regarding MAAEs attributed to study vaccine, AESIs and SAEs.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

- First episode of PCR-positive mild, moderate, or severe COVID-19, where severity is defined as:

Mild COVID-19 (≥1 of the following):

- Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
- New onset cough
- ≥2 additional COVID-19 symptoms:
    - New onset or worsening of shortness of breath or difficulty breathing compared to baseline
    - New onset fatigue
    - New onset generalized muscle or body aches
    - New onset headache
    - New loss of taste or smell
    - Acute onset of sore throat, congestion, or runny nose
    - New onset nausea, vomiting or diarrhea

OR Moderate COVID-19 (≥1 of the following):

- High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days)
- Any evidence of significant lower respiratory tract infection (LRTI):
    - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline)
    - Tachypnea: 24 to 29 breaths per minute at rest
    - SpO_2: 94% to 95% on room air
    - Abnormal chest X-ray or chest computerized tomography (CT) consistent with pneumonia or LRTI
- Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor).

OR Severe COVID-19 (≥1 of the following):

- Tachypnea: ≥30 breaths per minute at rest
- Resting heart rate ≥125 beats per minute
- SpO_2: ≤93% on room air or PaO_2/FiO_2 <300 mmHg
- High flow oxygen (O_2) therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure)
- Mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

- One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following:
    - Acute respiratory failure, including acute respiratory distress syndrome
    - Acute renal failure
    - Acute hepatic failure
    - Acute right or left heart failure
    - Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg)
    - Acute stroke (ischemic or hemorrhagic)
    - Acute thrombotic event: acute myocardial infarction, deep vein thrombosis (DVT), pulmonary embolism (PE)
    - Requirement for: vasopressors, systemic corticosteroids, or hemodialysis
- Admission to an intensive care unit (ICU)
- Death

Key Secondary Endpoint:

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

Other Secondary Endpoints:

- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
    - ANY symptomatic SARS-CoV-2 infection, defined as PCR-positive nasal swab and ≥1 of any of the following symptoms: (a) Fever; (b) New onset cough; (c) New onset or worsening of shortness of breath or difficulty breathing compared to baseline; (d) New onset fatigue. New onset generalized muscle or body aches; (f) New onset headache; (g) New loss of taste or smell; (h) Acute onset of sore throat, congestion, or runny nose; (i) New onset nausea, vomiting or diarrhea
- Neutralizing antibody titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.
- Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers from Immunogenicity Population at Days 0, 35 and immediately prior to administration of the crossover set of vaccinations.
- Serum IgG levels to SARS-CoV-2 S protein, MN_{50} and hACE2 inhibition titers from Immunogenicity Population at Months 12, 18, and 24.
- Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form.
    - Local reactogenicity: (a) Pain; (b) Tenderness; (c) Erythema; (d) Swelling/induration
    - Systemic reactogenicity: (a) Fever; (b) Malaise; (c) Fatigue; (d) Arthralgia; (e) Myalgia; (f) Headache; (g) Nausea/vomiting

- Incidence and severity of MAAEs and unsolicited AEs through 49 days, i.e., 28 days after second injection of each set of vaccinations (initial and crossover).
- Incidence and severity of MAAEs attributed to study vaccine, SAEs and AESIs through Month 12.
- Incidence and severity of SAEs, MAAEs attributed to study vaccine and AESIs during Month 12 through Month 24 or the EoS.
- Death due to any cause.
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, immediately prior to administration of the crossover set of vaccinations, and at Months 12, 18 and 24 will be used to determine natural infection and to determine the incidence of asymptomatic infection acquired during study follow-up.
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.
- IgG antibodies to SARS-CoV-2 rS at approximately 35 days after the first crossover vaccination in approximately 300 active vaccine recipients 18 to ≤64 years of age enrolled at selected study sites.
- Neutralizing antibody response at Day 35 for all adolescent participants seronegative to anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in seronegative adult participants 18 to <26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).

6.1.9 Statistical Considerations & Statistical Analysis Plan

The sample size for the original study design (i.e., no cross-over) in the Adult Main Study was driven by the total number of cases expected to achieve statistical significance for the primary efficacy endpoint; approximately 30,000 participants ≥18 years of age were enrolled to provide a target of 144 symptomatic PCR-confirmed SARS-CoV-2 infections. The Per-Protocol efficacy (PP-EFF) analysis sets included all participants who received the initial 2-dose regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 PCR-positive episode (i.e., participant was censored at the time of the protocol deviation) and were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding.

Although the study enrolled participants regardless of SARS-CoV-2 serologic status at the time of initial vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or serology, were excluded from the per-protocol efficacy (PP-EFF) population, which was the primary efficacy analysis population for the pre-crossover period.

The full analysis set (FAS) was used for supportive analyses; the FAS included all participants who were randomized and received at least 1 dose of study vaccine/placebo, regardless of protocol violations or missing data. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. The FAS population was analyzed according to the treatment group to which they were randomized.

The safety analysis sets included all participants who received at least 1 dose of trial vaccine. Participants in the safety analysis set were analyzed according to the vaccine actually received.

In cases where available information indicated that a participant received both active and placebo, the participant was analyzed as part of the active group.

In the Adult Main Study, the primary endpoint was analyzed on the PP-EFF analysis set and supported by analysis of the FAS analysis set. The VE was defined as VE (%) = (1 – RR) x 100, where RR = relative risk of incidence rates between the 2 trial vaccine groups (SARS-CoV-2 rS / Placebo). The RR was estimated by exponentiating the treatment group coefficient from a Poisson regression analysis with robust error variance. The age strata were included in the model as a covariate. To assess incidence rates rather than absolute counts of cases, an offset was utilized in the Poisson regression to account for differences in follow-up times starting with 7 days after the second vaccination among participants. A two-sided 95% confidence interval (CI) was constructed around the estimate.

Successful demonstration of VE was based on a hypothesis test with a one-sided Type I error of 2.5% conducted with the following hypotheses: H0: VE ≤0.30 (RR ≥0.70) and H1: VE >0.30 (RR <0.70). Rejection of the null hypothesis required a statistically significant VE with a lower bound of CI >30%.

In the Booster substudy, in the absence of an active or placebo control, the incidence of the defined COVID-19 illnesses during the post-booster follow-up was assessed to describe changes over time from pre-booster period to post-booster, impact on severity of illness and variants responsible for infections, as described in the Objectives specific to the Booster Amendment. Incidence rates of COVID-19 illness was summarized according to the timing of receipt of active vaccine (i.e., initial versus crossover dosing series).

In formal analyses, numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with solicited local and systemic AEs through 7 days after each dose of the initial set of vaccinations and the booster vaccination were summarized by trial vaccine group (overall for the booster) and by maximum toxicity grade over 7 days after each vaccination. The durations of solicited local and systemic AEs after each vaccination were also summarized by trial vaccine group but for the pre-booster vaccination and overall, for the booster period, the summary was for all participants. Reactogenicity was not systematically evaluated after crossover.

Unsolicited AEs were coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by trial vaccine group as well as by severity and relationship to trial vaccine. AEs through 28 days after second injection of each set of vaccinations (initial and crossover series); all MAAEs related to vaccine, SAE, or AESI through the end of the study were listed separately and summarized by trial vaccine group for the pre-booster period, and overall, for the booster period. Participants who were unblinded to treatment assignment were requested to report SAE, MAAE, AESIs and COVID-19 diagnoses by remote contact at the remaining prespecified time points following unblinding.

Participants who chose to be unblinded prior to the blinded crossover and received authorized/approved vaccine were followed for safety (SAE, MAAE, AESI, and COVID-19 diagnosis) by remote contact on the remaining schedule. For further information regarding statistical consideration, the reader is referred to the Statistical Review of the Novavax BLA..

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Adult Main Study 301 design is presented in the table below.

Table 3. Adult Main Study 301 Design

Trial Vaccine Group	Estimated Number of Randomized Participants[a]	Initial Day 0	Initial Day 21 (+7 days)	Crossover[b] Day 0	Crossover[b] Day 21 (+7 days)
SARS-CoV-2 rS (5 µg) + Matrix-M1 adjuvant (50 µg) N up to 20,000	18 to ≤64 years: ≤15,000 ≥65 years: ≥5,000	Vaccine	Active vaccine	Placebo	Placebo
Placebo (normal saline) N up to 10,000	18 to ≤64 years: ≤7,500 ≥65 years: ≥2,500	Placebo	Placebo	Active vaccine	Active vaccine

Source: Table 4, page 49 2019nCoV-301: Adult 17 Month Clinical Study Report
Abbreviations: SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; N=Number of randomized participants; µg=microgram
a. Availability of other COVID-19 vaccines under EUA may impact the possibility of enrolling certain age categories.
b. Following accrual of sufficient efficacy and safety data to support application for EUA, participants will be scheduled for administration of 2 injections of the alternate study material 21 days apart ("blinded crossover").

6.1.10.1.1 Demographics

The table below presents the demographic representation of study participants who enrolled in Adult Main Study 301 and were randomized to a two-dose series of Original Monovalent or placebo, pre-crossover, for the Safety Analysis Set.

Table 4. Demographics and Other Baseline Characteristics for Participants in the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Characteristic	Original Monovalent N=19735	Placebo N=9847	Total N=29582
Age (years)	--	--	--
Mean (SD)	46.5 (15.05)	46.8 (14.95)	46.6 (15.02)
Median	47.0	47.0	47.0
Minimum, maximum	18, 95	18, 90	18, 95
Age group, n (%)	--	--	--
18 to <65 years	17255 (87.4)	8612 (87.5)	25867 (87.4)
≥65 years	2480 (12.6)	1235 (12.5)	3715 (12.6)
Sex, n (%)	--	--	--
Male	10367 (52.5)	5019 (51.0)	15386 (52.0)
Female	9368 (47.5)	4828 (49.0)	14196 (48.0)
Race, n (%)	--	--	--
White	14795 (75.0)	7381 (75.0)	22176 (75.0)
Black or African American	2322 (11.8)	1164 (11.8)	3486 (11.8)
American Indian or Alaska Native[a]	1309 (6.6)	660 (6.7)	1969 (6.7)
Asian	809 (4.1)	416 (4.2)	1225 (4.1)
Multiple	326 (1.7)	160 (1.6)	486 (1.6)
Native Hawaiian or other Pacific Islander	56 (0.3)	12 (0.1)	68 (0.2)
Not Reported	110 (0.6)	47 (0.5)	157 (0.5)
Missing	8 (<0.1)	7 (<0.1)	15 (<0.1)

Characteristic	Original Monovalent N=19735	Placebo N=9847	Total N=29582
Ethnicity, n (%)	--	--	--
Hispanic or Latino	4333 (22.0)	2155 (21.9)	6488 (21.9)
Not Hispanic or Latino	15346 (77.8)	7669 (77.9)	23015 (77.8)
Not Reported	32 (0.2)	19 (0.2)	51 (0.2)
Unknown	22 (0.1)	3 (<0.1)	25 (<0.1)
Missing	2 (<0.1)	1 (<0.1)	3 (<0.1)
BMI (kg/m^2) category, n (%)	--	--	--
Underweight (<18.0 kg/m^2)	134 (0.7)	59 (0.6)	193 (0.7)
Normal (18.0 – 24.9 kg/m^2)	5740 (29.1)	2832 (28.8)	8572 (29.0)
Overweight (25.0 – 29.9 kg/m^2)	6359 (32.2)	3187 (32.4)	9546 (32.3)
Obese (≥30.0 kg/m^2)	7402 (37.5)	3729 (37.9)	11131 (37.6)
Missing	100 (0.5)	40 (0.4)	140 (0.5)
Occupation, n (%)	--	--	--
Currently working	13454 (68.2)	6705 (68.1)	20159 (68.1)
Working in close proximity to others	7796 (39.5)	3798 (38.6)	11594 (39.2)
Student attending school in person	1132 (5.7)	518 (5.3)	1650 (5.6)
In-person schooling/currently working/ working in close proximity to others, n (%)	13849 (70.2)	6906 (70.1)	20755 (70.2)
Days/week at workplace, n (%)	--	--	--
0 days/week	3055 (15.5)	1610 (16.4)	4665 (15.8)
1 day/week	955 (4.8)	447 (4.5)	1402 (4.7)
2 – 4 days/week	3411 (17.3)	1728 (17.5)	5139 (17.4)
≥5 days/week	6007 (30.4)	2913 (29.6)	8920 (30.2)
PPE used by people at workplace	10265 (52.0)	5074 (51.5)	15339 (51.9)
Living situation, mean (SD)	--	--	--
Number of people living with participant	2.0 (3.65)	1.9 (3.28)	2.0 (3.53)
Number of co-habitants under 18 years	0.6 (1.77)	0.6 (1.38)	0.6 (1.65)
Number of co-habitants 18 to <65 years	1.2 (2.71)	1.2 (3.01)	1.2 (2.81)
Number of co-habitants ≥65 years	0.2 (0.46)	0.2 (0.45)	0.2 (0.46)
Number attending school living with participant	0.5 (1.92)	0.5 (2.93)	0.5 (2.31)
Country, n (%)	--	--	--
U.S.	18559 (94.0)	9259 (94.0)	27818 (94.0)
Mexico	1176 (6.0)	588 (6.0)	1764 (6.0)
High-risk adults[b], n (%)	--	--	--
Yes	18812 (95.3)	9380 (95.3)	28192 (95.3)
No	923 (4.7)	467 (4.7)	1390 (4.7)
Comorbidities, n (%)	--	--	--
Obesity (BMI ≥30 kg/m^2)	7287 (36.9)	3667 (37.2)	10954 (37.0)
Chronic lung disease	2796 (14.2)	1455 (14.8)	4251 (14.4)
Diabetes mellitus type 2	1531 (7.8)	817 (8.3)	2348 (7.9)
Cardiovascular disease	230 (1.2)	129 (1.3)	359 (1.2)
Chronic kidney disease	150 (0.8)	68 (0.7)	218 (0.7)
Baseline serostatus, n (%)	--	--	--
Seronegative and PCR negative	18461 (93.5)	9156 (93.0)	27617 (93.4)
Seropositive and PCR positive	1274 (6.5)	691 (7.0)	1965 (6.6)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Page 26, Table 9
Abbreviations: BMI=body mass index; eCRF=electronic case report form; PCR=polymerase chain reaction; PPE=personal protective equipment; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD=standard deviation; U.S.=United States; N=All participants who received at least 1 dose of study product. For the

Vaccine Group, participants received at least 1 dose of study vaccine. For the Placebo Group, participants received only placebo during the pre-crossover period; n=number of subjects with the specified characteristic; kg/m^2=kilogram per square meter
a. American Indians were denoted as Native Americans in the eCRF; approximately 60% of Native Americans were enrolled at sites in Mexico, while ~40% were American Indians enrolled at sites in the U.S.
b. High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances.

Clinical Reviewer Comment: Demographics and baseline characteristics of participants in the Safety Analysis Set during the Pre-Crossover period were well balanced between the Original Monovalent and placebo groups (Table 4). Median age was 47.0 years. Approximately 13% of participants were ≥65 years of age and approximately half (48.0%) were female. The majority of participants were white (75.0%), not of Hispanic or Latino origin (77.8%), and located in the U.S. (94.0%). The majority of participants were overweight or obese (69.9%), with more than a third being obese. Most participants (95.3%) were categorized as high-risk adults for acquiring or experiencing complications of COVID-19, and 93.4% of participants had a seronegative (based on anti-NP serology) and PCR negative (based on negative nasal swab PCR) baseline status prior to randomization. In general, the demographic characteristics of the enrolled population were representative of the overall U.S. population; therefore, the results of the study were generalizable to the U.S. population at that time.

The table below presents the demographic representation of study participants who continued on to treatment in the blinded crossover vaccination period in the adult portion of Study 2019nCoV for the Safety Analysis Set.

Demographic and other baseline characteristics for those participants who continued on to treatment in the blinded crossover vaccination period were comparable to those included in the initial vaccination period. The median age was 46.0 years, with participants ranging in age from 18 to 95 years, with 11.3% participants ≥65 years of age. Approximately half the participants were male and half female. The majority (73.9%) were White, not of Hispanic or Latino origin (76.9%) and located in the U.S. (93.5%). The majority of participants were overweight or obese (71.0%), with more than a third being obese. Most participants (95.4%) were categorized as high-risk adults for acquiring or experiencing complications of COVID-19, and most (93.0%) had a seronegative (based on anti-NP serology) and PCR negative (based on negative nasal swab PCR) baseline status prior to randomization. Note that roughly 8,000 fewer participants continued on to the blinded crossover compared with the original 2 dose series.

The table below summarizes demographic representation of study participants who continued on to treatment in the booster vaccination period in the adult portion of Study 2019nCoV for the Safety Analysis Set.

Clinical Reviewer Comment: The demographic characteristics of the Safety Analysis Set were comparable to those observed in the blinded crossover vaccine period.

6.1.10.1.3 Participant Disposition

The study disposition of all randomized participants before and after crossover are presented in the two tables below. Overall, few participants were discontinued or lost to follow-up and these discontinuations were generally balanced between treatment groups.

Table 5. Study Disposition for the Initial Vaccination Period, All Randomized Participants

Disposition	Original Monovalent n (%)	Placebo n (%)	Total n (%)
Randomized	19961	9982	29943
Treated	19714	9868	29582
Completed 1 dose	19714 (100)	9868 (100)	29582 (100)
Completed 2 doses	19087 (96.8)	9440 (95.7)	28527 (96.4)
Discontinued on/after Dose 1 but before Dose 2	561 (2.8)	386 (3.9)	947 (3.2)
Reason for discontinuation	--	--	--
Withdrawal by participant	316 (1.6)	257 (2.6)	573 (1.9)
Lost to follow-up	200 (1.0)	102 (1.0)	302 (1.0)
Other	25 (0.1)	21 (0.2)	46 (0.2)
Adverse event	18 (<0.1)	3 (<0.1)	21 (<0.1)
Death	2 (<0.1)	3 (<0.1)	5 (<0.1)
Discontinued on/after Dose 2	2567 (13.0)	2345 (23.8)	4912 (16.6)
Reason for discontinuation	--	--	--
Withdrawal by participant	1639 (8.3)	1609 (16.3)	3248 (11.0)
Lost to follow-up	808 (4.1)	628 (6.4)	1436 (4.9)
Other	109 (0.6)	100 (1.0)	209 (0.7)
Adverse event	2 (<0.1)	3 (<0.1)	5 (<0.1)
Death	9 (<0.1)	5 (<0.1)	14 (<0.1)
Discontinued from initial vaccination period	3128 (15.9)	2731 (27.7)	5859 (19.8)
Reason for discontinuation	--	--	--
Withdrawal by participant	1955 (9.9)	1866 (18.9)	3821 (12.9)
Lost to follow-up	1008 (5.1)	730 (7.4)	1738 (5.9)
Other	134 (0.7)	121 (1.2)	255 (0.9)
Adverse event	20 (0.1)	6 (<0.1)	26 (<0.1)
Death	11 (<0.1)	8 (<0.1)	19 (<0.1)

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report, Table 17, Pages 99-100
Note: Denominators are the number of treated participants; n=number of unique subjects for each category.
Note: Treatment group reflects treatment assignment at randomization

Table 6. Study Disposition Blinded Crossover Vaccination Period, All Randomized Participants, Adult Main Study 301

Disposition	Original Monovalent to Placebo n (%)	Placebo to Original Monovalent n (%)	Total n (%)
Did not receive Original Monovalent or placebo	4395	3473	7868
Crossed over to receive Original Monovalent or placebo	15319 (100)[a]	6395 (100)[a]	21714 (100)[a]
Completed Dose 3	15319 (100)	6395 (100)	21714 (100)
Completed Dose 4	15104 (98.6)	6328 (99.0)	21432 (98.7)
Discontinued on/after Dose 3 but before Dose 4	183 (1.2)	56 (0.9)	239 (1.1)
Reason for discontinuation	--	--	--
Withdrawal by participant	82 (0.5)	18 (0.3)	100 (0.5)
Lost to follow-up	84 (0.5)	35 (0.5)	119 (0.5)
Other	12 (<0.1)	2 (<0.1)	14 (<0.1)
Death	3 (<0.1)	0	3 (<0.1)
Adverse event	2 (<0.1)	1 (<0.1)	3(<0.1)

Disposition	Original Monovalent to Placebo n (%)	Placebo to Original Monovalent n (%)	Total n (%)
Discontinued on/after Dose 4	3585 (23.4)	1264 (19.8)	4849 (22.3)
Reason for discontinuation	--	--	--
Withdrawal by participant	2070 (13.5)	647 (10.1)	2717 (12.5)
Lost to follow-up	1350 (8.8)	538 (8.4)	1888 (8.7)
Other	136 (0.9)	66 (1.0)	202 (0.9)
Death	27 (0.2)	10 (0.2)	37 (0.2)
Adverse event	2 (<0.1)	3 (<0.1)	5 (<0.1)
Discontinued from blinded crossover vaccination period	3768 (24.6)	1320 (20.6)	5088 (23.4)
Reason for discontinuation	--	--	--
Withdrawal by participant	2152 (14.0)	665 (10.4)	2817 (13.0)
Lost to follow-up	1434 (9.4)	573 (9.0)	2007 (9.2)
Other	148 (1.0)	68 (1.1)	216 (1.0)
Death	30 (0.2)	10 (0.2)	40 (0.2)
Adverse event	4 (<0.1)	4 (<0.1)	8 (<0.1)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Page 16, Table 3
a. Denominator is number of participants dosed in the period.
Note: N=number of treated participants in period; n=number of unique subjects for each category.
Note: Treatment group reflects treatment assignment at randomization

During the initial vaccination period, 29,582 participants received at least 1 dose of study material (Original Monovalent or placebo), with 19,714 in the Original Monovalent group and 9,868 in the placebo group as randomized (Table 5). Approximately 96% of treated participants received both vaccinations in the initial vaccination period. A total of 5,859 (19.8%) participants discontinued the study prior to the blinded crossover vaccination period, with 3,128 (15.9%) in the Original Monovalent group and 2,731 (27.7%) in the placebo group. The most frequent (incidence >1%) reasons for study discontinuation were withdrawal by participant (12.9%) and lost to follow-up (5.9%); for each of these reasons, a higher percentage of placebo recipients than Original Monovalent recipients discontinued the study. One reason for this discrepancy was the receipt of an EUA-approved COVID-19 vaccine.

The blinded crossover vaccination period was initiated on 20 April 2021. During the blinded crossover vaccination period, 15,319 (77.7%) participants who received Original Monovalent during the initial vaccination period crossed over to receive placebo (Original Monovalent to placebo) and 6,395 (64.8%) participants who had received placebo crossed over to receive Original Monovalent (placebo to Original Monovalent), with nearly 99% of participants who crossed over receiving both doses of trial vaccine (Table 6). A total of 5,088 (23.4%) participants discontinued the study during the blinded crossover vaccination period, with 3,768 (24.6%) participants in the Original Monovalent to placebo group and 1,320 (20.6%) in the placebo to Original Monovalent group. A total of 239 (1.1%) participants discontinued the study after Dose 3 but on or before the Dose 4 administration date and 4,849 (22.3%) participants discontinued the study after Dose 4. The most frequent (incidence >1%) reasons for study discontinuation were withdrawal by participant (13.0%) and lost to follow-up (9.2%).

Clinical Reviewer Comment: One reason that a higher percentage of participants discontinued in the placebo group compared with the vaccine group during the initial vaccination period (Table 5) was the availability of another authorized COVID-19 vaccine. In general, this imbalance did not substantively affect the outcome of this study during the initial vaccination period. For the crossover period, few participants discontinued or were lost to follow-up, and these discontinuations were generally balanced between treatment groups.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

On April 1, 2024, Novavax submitted an addendum to their Adult 17 Month Clinical Study Report, with supporting datasets which were adjusted in accordance with FDA advice to ensure adequate dataset organization for an effective review. These dataset adjustments resulted in slight changes to some of the efficacy analyses. The Adult 17 Month Clinical Study Report Addendum report and datasets were used to analyze the vaccine efficacy for Adult Main Study 301 in this review. Although the numbers for some of these analyses differed from what was originally reviewed under EUA, the changes were minimal and did not alter the review team's assessment of vaccine efficacy for the two-dose series of the Original Monovalent vaccine in previously unvaccinated individuals.

The primary endpoint was the first episode of PCR-confirmed mild, moderate, or severe COVID-19. The analysis was based on the Per-Protocol Efficacy Set. At the time of the data cutoff date (18 August 2022) for the addendum to Adult 17 Month Clinical Study Report, following further revisions to the Adult Main Study 301 datasets, a total of 94 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in the initial vaccination period had accrued in the PP-EFF Analysis Set. Of these cases, 18 (0.10%) participants were in the Original Monovalent group and 76 (0.91%) were in the placebo group. All 18 cases in the Original Monovalent group were mild in severity. In the placebo group, 64 cases were mild, 8 were moderate, and 4 were severe. The resultant VE of Original Monovalent to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative adult participants was 89.6% (95% CI: 82.5, 93.8) using the Poisson regression model. Supportive analysis using the Cox proportional hazard model resulted in a VE of 89.7 % (95% CI: 82.7, 93.8). VE against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after the second vaccination of the initial vaccination period in serologically negative adult participants is summarized in the table below.

Table 7. Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 With Onset From at Least 7 Days After Second Vaccination of the Initial Vaccination Period in Serologically Negative Adult Participants, PP-EFF Analysis Set, Adult Main Study 301

Parameter	Original Monovalent N=17184	Placebo N=8326
Participants with no occurrence of case[a], n (%)	17166 (99.9)	8250 (99.1)
Participants with occurrence of case[b], n (%)	18 (0.1)	76 (0.9)
Severity of first occurrence, n (%)	--	--
Mild	18 (0.1)	64 (0.8)
Moderate	0	8 (0.1)
Severe	0	4 (0.05)
Median surveillance time[c] (days)	63.0	57.0
Log-linear model using modified Poisson regression[d]	--	--
Mean incidence rate per year in 1000 people	6.0	57.2
95% CI	3.7, 9.5	45.7, 71.6
Relative risk	0.1	--
95% CI	0.1, 0.2	--
Vaccine efficacy (%)	**89.6**	--
95% CI	**82.5, 93.8**	--

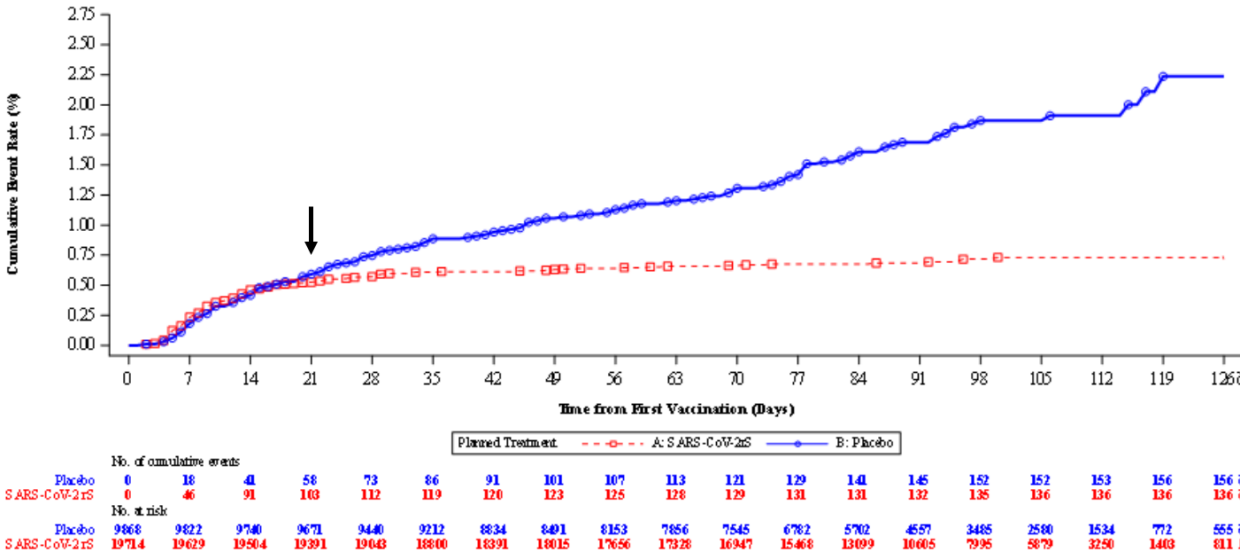
Parameter	Original Monovalent N=17184	Placebo N=8326
Cox proportional hazard model (supportive analysis)[e]	--	--
Vaccine efficacy (%)	89.7	--
95% CI	82.7, 93.8	--

Source: 301 17 month CSR Addendum Table 15, Page 49
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; LSMEANS=least squared means; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy; VE=vaccine efficacy; N=PP-EFF analysis set; n=number of unique subjects for each category.
a. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria.
b. Case=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
c. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of case/ censoring) and date at start of surveillance period (7 days after the Second Injection) + 1.
d. Modified Poisson regression with logarithmic link function, vaccine group and age strata as fixed effects and robust error variance (Zou, 2004). Mean incidence was calculated with weighting for 18 to <65 years of age and ≥65 years of age groups reflective of the distribution seen in the study population (i.e., observed margins [OM] option for LSMEANS statement in SAS PROC GENMOD).
e. Cox-proportional hazard model with Efron's method for tie handling with vaccine group and age strata as covariates. Hazard ratio was used to estimate relative risk.

> *Clinical Reviewer Comment: Vaccine efficacy for the Original Monovalent vaccine was approximately 90 percent which was substantial, and similar to the efficacy originally seen for the Pfizer and Moderna vaccines. This clinical evidence forms the basis for inferring that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is effective.*

The cumulative incidence curve for adults regardless of vaccine status who developed mild, moderate, or severe COVID-19 after the first vaccination during the initial vaccination period is displayed in Figure 1.

Figure 1. Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From First Vaccination of the Initial Vaccination Period in Adult Participants Who Received at Least 1 Dose of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) Regardless of Baseline Serostatus, Adult Main Study 301



Source: 301 17 month CSR Addendum Figure 1, Page 69
Abbreviations: COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction
Within figure SARS-CoV-2 rS represents Original Monovalent.
Case=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset from first injection within the surveillance period, which is defined as first vaccination through the date of data cut or censoring event.
Participants were censored at the earliest of 1) cut-off date (18 August 2022); 2) date of death; 3) date of unblinding (including for intended receipt of alternative COVID-19 vaccine); 4) early withdrawal *end of follow-up*; 5) first dose of crossover; or 6) date of booster dose.
Arrow represents when the second dose was administered, 21 days after first dose.

> *Clinical Reviewer Comment: COVID-19 onset occurred similarly for both the SARS-CoV-2rS and placebo groups until approximately 21 days after Dose 1, at which time point, the curves diverged. This finding supports an assertion that active vaccination is associated with decreased COVID-19 disease incidence in the actively vaccinated participants as compared with the placebo participants.*

6.1.11.2 Analyses of Secondary Endpoints

VE against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered as a variant of concern or variant being monitored (December 2021 CDC Classification) with onset from at least 7 days after second vaccination of the initial vaccination period in serologically negative adult participants using the PP-EFF analysis set is summarized in the table below.

Table 8. Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 Due to a SARS-CoV-2 Variant Considered as a Variant of Concern or Variant Being Monitored (December 2021 CDC Classification) With Onset From at Least 7 Days After Second Vaccination of the Initial Vaccination Period in Serologically Negative Adult Participants, PP-EFF Analysis Set, Adult Main Study 301

Parameter	Original Monovalent N=17184	Placebo N=8326
Participants with no occurrence of case[a], n (%)	17176 (100.0)	8276 (99.4)
Participants with occurrence of case[b], n (%)	8 (0.05)	50 (0.6)
Severity of first occurrence, n (%)	--	--
Mild	8 (0.05)	42 (0.5)
Moderate	0	6 (0.1)
Severe	0	2 (0.02)
Median surveillance time[c] (days)	63.0	57.0
Log-linear model using modified Poisson regression[d]	--	--
Mean incidence rate per year in 1000 people	2.5	35.7
95% CI	1.2, 5.2	26.6, 47.8
Relative risk	0.1	--
95% CI	0.03, 0.2	--
Vaccine efficacy, %	**92.9**	--
95% CI	**85.1, 96.7**	--

Source: 301 17 month CSR Addendum Table 18, Page 58
Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; COVID-19=coronavirus disease 2019; LSMEANS=least squared means; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy; n=number of unique subjects for each category.
a. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria and not considered a VOC or VOI.
b. Case=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 due to a VOC or VBM with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
c. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of case/censoring) and date at start of surveillance period (7 days after the Second Injection)+1.
d. Modified Poisson regression with logarithmic link function, vaccine group and strata as fixed effects and robust error variance (Zou, 2004). Mean incidence was calculated with weighting for 18 to <65 years of age and ≥65 years of age groups reflective of the distribution seen in the study population (i.e., observed margins [OM] option for LSMEANS statement in SAS PROC GENMOD).
Note: VOC/VBM were established by SIG and CDC for SARS-CoV-2 Variant Classifications and Definitions for December 2021 [CDC 2022].

In the PP-EFF analysis set, there were 58 cases (8 [0.05%] in the Original Monovalent group and 50 [0.6%] in the placebo group) of SARS-CoV2 with mutations that would identify them as a VOC (variant of concern) or VBM (variant being monitored). All 8 cases in the Original Monovalent group were mild in severity, whereas in the placebo group, 8 of 50 cases were moderate or severe. The resultant VE of Original Monovalent to prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered a VOC or VBM in baseline seronegative adult participants was 92.9% (95% CI: 85.1, 96.7).

Clinical Reviewer Comment: Vaccine efficacy against variants of concern was supported by this secondary endpoint analysis which was descriptive in nature.

6.1.11.3 Subpopulation Analyses

VE estimates in the subgroups were generally consistent with the overall VE (89.6% [95% CI: 82.5, 94.8]). However, some of the demographic groups had too few cases of COVID-19 to draw any conclusions on these data. The subgroup analyses of VE against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination of the initial vaccination period in serologically negative adult participants is summarized in the table below.

Table 9. Subgroup Analyses of Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 With Onset From at Least 7 Days After Second Vaccination of the Initial Vaccination Period in Serologically Negative Adult Participants, PP-EFF Analysis Set, Adult Main Study 301

Characteristic	Original Monovalent Cases[a]/N (%) (Mean Incidence Rate/1,000 Person-Years)[b]	Placebo Cases[a]/N (%) (Mean Incidence Rate/1,000 Person-Years)[b]	Vaccine Efficacy[b] (95% CI)
Age	--	--	--
18 to <65 years	15/15162 (0.0) (5.7)	72/7365 (1.0) (61.8)	90.8 (83.9, 94.7)
≥65 years	3/2022 (0.1) (8.6)	4/961 (0.4) (26.8)	68.0 (-43.01, 92.8)
50 to <65 years	4/5525 (0.1) (4.2)	17/2809 (0.6) (39.3)	89.2 (67.9, 96.4)
High-risk condition[c]	--	--	--
No	1/811 (0.1) (7.1)	1/405 (0.2) (16.3)	56.1 (-3342.8, 99.4)
Yes	17/16373 (0.1) (5.9)	75/7921 (0.9) (59.1)	90.0 (83.1, 94.1)
Sex	--	--	--
Male	8/8950 (0.1) (5.1)	28/4204 (0.7) (42.3)	87.9 (73.4, 94.5)
Female	10/8234 (0.1) (6.8)	48/4122 (1.2) (71.4)	90.4 (81.1, 95.2)
Race (summary)	--	--	--
White	14/13059 (0.1) (6.3)	57/6311 (0.9) (59.4)	89.4 (80.9, 94.1)
Non-White	4/4026 (0.1) (5.3)	18/1971 (0.9) (51.4)	89.7 (69.6, 96.5)
Race (individual)	--	--	--
White	14/13059 (0.1) (6.3)	57/6311 (0.9) (59.37)	89.4 (80.9, 94.1)
Black or African American	1/1878 (0.05) (3.0)	8/941 (0.9) (49.4)	94.0 (51.9, 99.3)
American Indian or Alaska Native[d]	1/1056 (0.1) (4.4)	6/511 (1.2) (55.6)	92.1 (34.8, 99.1)
Asian	0/750 (0) (0.0)	4/373 (1.1) (69.4)	100.0 (33.5, 100.0) 5
Native Hawaiian or other Pacific Islander	0/47 (0) (0.0)	0/10 (0) (0.0)	NE[e]
Multiple	2/295 (0.7) (39.1)	0/136 (0) (0.0)	NE[e]
Ethnicity	--	--	--
Hispanic or Latino	9/3672 (0.2) (13.1)	18/1782 (1.01) (57.7)	77.4 (49.6, 89.8)
Not Hispanic or Latino	9/13473 (0.1) (3.9)	58/6532 (0.9) (57.8)	93.2 (86.3, 96.6)
Country	--	--	--
U.S.	17/16187 (0.1) (6.1)	72/7838 (0.9) (59.3)	89.7 (82.5, 93.9)
Mexico	1/997 (0.1) (4.3)	4/488 (0.8) (36.1)	88.1 (-6.0, 98.7)

Characteristic	Original Monovalent Cases[a]/N (%) (Mean Incidence Rate/1,000 Person-Years)[b]	Placebo Cases[a]/N (%) (Mean Incidence Rate/1,000 Person-Years)[b]	Vaccine Efficacy[b] (95% CI)
Comorbidity status[f]	--	--	--
Chronic lung disease	1/2474 (0.04) (2.4)	9/1266 (0.7) (45.4)	94.8 (58.6, 99.4)
Cardiovascular disease	1/203 (0.5) (29.2)	2/104 (1.9) (122.0)	76.04 (-360.3, 99.6)
Diabetes	1/1300 (0.1) (4.3)	5/694 (0.7) (43.6)	90.1 (16.1, 98.8)
BMI >30	6/6320 (0.1) (5.3)	33/3134 (1.1) (61.6)	91.5 (79.6, 96.4)
Chronic renal disease	1/123 (0.8) (47.3)	1/60 (1.7) (101.7)	53.6 (-3546.5, 99.4)
Chronic liver disease	1/103 (0.971) (57.7)	0/49 (0) (0.0)	NE
HIV	0/134 (0) (0.0)	1/49 (2.04) (127.4)	100.0 (-1294.0, 100.0)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR Novavax Confidential, Table 16, Page 54 and Table 13 Page 34, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR

Abbreviations: BMI=body mass index; CI=confidence interval; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; LSMEANS=least squared means; NE=not estimable in the event the test for exact binomial proportion cannot be conducted; NP=nucleoprotein; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; PCR=polymerase chain reaction; RR=relative risk; U.S.=United States; VE=vaccine efficacy; HIV=human immunodeficiency virus N=PP-EFF; n=number of unique subjects for each category.

a. Case=First occurrence of PCR-confirmed mild, moderate or severe COVID-19 with onset from 7 days after second injection within the surveillance period.

b. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of trial vaccine (Original Monovalent or placebo) in the initial vaccination period. RR is ratio of incidence rates of active group relative to the placebo group (Original Monovalent/placebo) with first occurrence of case with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cut-off date (18 August 2022), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) end of follow-up, or (vi) first dose of blinded crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 criteria were censored at date of the PCR-positive.

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

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

e. In cases where there are zero cases in either vaccine group or the total number of cases in both vaccine groups combined <5, VE and 95% CI is calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases and is adjusted for total surveillance time.

f. Comorbidities included obesity (BMI >30 kg/m, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and/or chronic kidney disease

Note: Mean incidence rate and RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, vaccine group and age strata as fixed effects and robust error variance (Zou, 2004). By age group summaries included vaccine group only as a fixed effect. Mean incidence was calculated with weighting for 18 to <65 years of age and ≥65 years of age groups reflective of the distribution seen in the study population (i.e., observed margins [OM] option for LSMEANS statement in SAS PROC GENMOD). (If all cases occurred in only one age group in the specified subgroup, only vaccine group as fixed effect).

Immunogenicity Endpoints

A third dose of Original Monovalent was administered at a median of 10.1 months (minimum of 7 months and maximum of 13 months) after the second dose of Original Monovalent in adult participants included within the Booster Per-Protocol Set for immunogenicity analysis (PP-IMM) Analysis Set. The lower bound (LB) of the 95% CI for the ratio of neutralizing antibody geometric mean titers (GMTs) (GMFR: 2.7), was above the predefined noninferiority criterion of 1.0 for the original analysis which is summarized in the table below.

Table 10. Ratio of Neutralizing Antibody Titers (MN_{50}) Against SARS-CoV-2 Wild-Type Virus (Ancestral Wuhan Strain) at 28 Days After the Booster Dose of Original Monovalent Versus at 14 Days after the Second Dose of Original Monovalent in the Primary Series in Serologically Negative Adult Participants, Booster PP-IMM Analysis Set, Adult Main Study 301

Original Monovalent Booster N=222 GMT (95% CI)[a]	Original Monovalent Primary Series N=222 GMT (95% CI)[a]	GMFR Booster/Primary Series (95% CI)[a]	Evaluation[b]
4947.1 (4315.6, 5671.1)	1553.4 (1277.3, 1889.1)	3.2 (2.7, 3.8)	LB of 95% CI >1.0 criterion: Yes

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report Table 90, page 228
Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; LB=lower bound; MN_{50}=microneutralization assay with an inhibitory concentration of 50%; PP-IMM=Per-Protocol Immunogenicity
a. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
b. Noninferiority of the single booster dose of Original Monovalent for the original analysis was defined as achieving the LB of the 95% CI for the ratio of MN_{50} GMT at 28 days after a single booster dose versus 14 days after the second dose of Original Monovalent >1.0.

The neutralizing antibody SCR against the wild-type virus (ancestral Wuhan strain) 28 days after the booster dose of Original Monovalent relative to the time of the booster dose was 92.3%, which was lower than that reported at 14 days after the primary series of Original Monovalent (94.1%). The LB of the 95% CI for the difference between post booster and post primary series in neutralizing antibody SCRs (-6.1%) was above the prespecified noninferiority criterion for the original analysis (-10%), indicating that the immune response from the third dose was consistent with the immune response following the initial two dose series. The noninferiority analysis between the SCRs after the initial two-dose series and the third vaccine dose is summarized in the table below.

Table 11. Seroconversion Rates for Neutralizing Antibody Titers (MN_{50}) Against SARS-CoV-2 Wild-Type Virus (Ancestral Wuhan Strain) at 28 Days after the Booster Dose of Original Monovalent Relative to the Time of Booster Vaccination Versus at 14 Days after the Second Dose of Original Monovalent (Primary Series) Relative to the Time of First Vaccination in Serologically Negative Adult Participants, Booster PP-IMM Analysis Set, Adult Main Study 301

Original Monovalent Booster N=222 SCR, n (%) (95% CI)[a]	Original Monovalent Primary Series N=222 SCR, n (%) (95% CI)[a]	Difference in SCR[b] Booster-Primary Series (95% CI)[c]	Evaluation[d]
205 (92.3) (88.0, 95.5)	209 (94.1) (90.2, 96.8)	-1.8 (-6.1, 2.3)	LB of 95% CI >-10% criterion: Yes

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report Table 91, page 230
Abbreviations: CI=confidence interval; LB=lower bound; MN50=microneutralization assay with an inhibitory concentration of 50%; PP-IMM=Per-Protocol Immunogenicity; SCR=seroconversion rate.;N=Booster PP-IMM Analysis Set. Included subjects who received 2 doses of the active vaccine either in the initial vaccination period or in the blinded crossover vaccination period, had a blood sample collected at the day of the first active dose, at Day 35 after the primary series, did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose, did not receive an emergency use authorized COVID-19 vaccine, received the booster dose, did not unblind, and did not have major protocol deviations through 7 days post-crossover Dose 2; n=number of unique subjects for each category.
a. Based on Clopper-Pearson.
b. Comparison between SCR of 28 days post-booster relative to time of booster and SCR of 14 days after second dose of Original Monovalent relative to time of first dose of Original Monovalent.
c. Tango method.
d. Noninferiority of the single booster dose of Original Monovalent for the original analysis was defined as achieving the LB of the 95% CI for the difference of the percentage of participants with SCR in MN_{50} titers at 28 days after a single

booster dose relative to the time of booster vaccination of Original Monovalent versus at 14 days after the second dose of Original Monovalent relative to the time of first vaccination of Original Monovalent is >-10%.
Note: The SCR percentage was defined as percentage of participants at the post vaccination visit with a ≥4-fold rise from baseline if baseline is equal to or above LLOQ, or at least 4-fold rise from LLOQ if baseline is below LLOQ in antibody concentration.

6.1.11.4 Dropouts and/or Discontinuations

The number of participants who dropped out and/or discontinued from the study did not affect the interpretation of the vaccine efficacy outcomes. Refer to Section 6.1.12.7 for details regarding dropouts and/or discontinuations.

6.1.12 Safety Analyses

6.1.12.1 Methods

The available safety analysis population consisted of N=29,582, which included 19,735 recipients of at least one dose of the Original Monovalent and 9,847 placebo recipients during the initial vaccination. Safety follow-up evaluations were planned through 24 months post-last dose of the primary series.

Safety assessments included the following:

- Solicited local and systemic reactogenicity through 7 days following vaccination, pre-crossover.
- Unsolicited adverse events (AEs), both pre- and post-crossover, from Dose 1 through the 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo. Unsolicited adverse events were also assessed in the booster period.
- Medically attended AEs (MAAEs), both pre- and post-crossover, from Dose 1 through the 28 days post Dose 2; participants who only received the first dose in the pre- and post-crossover periods were monitored for non-serious unsolicited adverse events through 49 days after administration of vaccine or placebo or if only Dose 1 is provided then 49 days after Dose 1. MAAEs was also assessed during the booster period.
- MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest for the pre- and post-crossover and booster periods, for the duration of the study in all participants.
- Deaths – were assessed in the pre-crossover, post-crossover, and booster periods.
- Nonfatal serious adverse events were assessed in the pre-crossover, post-crossover, and booster periods.
- AEs leading to vaccine discontinuation and study withdrawal for the pre- and post-crossover periods.
- Adverse events of special interest, evaluated by Applicant-generated SMQ analyses during the pre-crossover period.

Solicited local and systemic ARs with onset within 7 days after vaccination are presented in the tables below for participants in the Safety Analysis Set, stratified by age (18 through 64 years; ≥65 years).

Data collected in the pre-crossover period are placebo-controlled, whereas data collected in the post-crossover and booster periods are open-label, limiting comparisons between the treatment

arms. Participants who were unblinded for the purpose of receiving an approved/authorized vaccine, were encouraged to remain in the study for safety follow-up as defined in the protocol, and safety assessments were performed via the timelines and mechanisms as described in the protocol. In addition, investigators were required to report any TEAEs observed in participants who received another manufacturer's approved/authorized vaccine to health care and/or regulatory authorities via the local Regulatory reporting guidance.

6.1.12.2 Overview of Adverse Events

Overview of Adverse Events

The safety analyses presented in this review are derived from safety data (see preceding section), and deaths obtained during the pre-crossover, post-crossover, and booster periods of Adult Main Study 301, with a database cutoff date of August 18, 2022.

Solicited Adverse Events

Solicited adverse events through the cutoff date of August 18, 2022, are presented in this section. The tables were updated based on dataset reformatting that was recommended by the Division.

Local Adverse Reactions

The frequency and percentage of solicited local injection site TEAEs within 7 days after each dose of the initial vaccination period by maximum severity in the Safety Analysis Set is presented in the table below.

Table 12. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Each Dose in the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=18334 n (%)	Placebo Dose 1 N=9106 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Placebo Dose 2 N=8916 n (%)
Any solicited local injection site TEAE	--	--	--	--
Any (Grade ≥1)	10608 (57.9)	1926 (21.2)	13668 (74.6)	1824 (20.5)
Grade 3	194 (1.1)	21 (0.2)	1134 (6.2)	24 (0.3)
Grade 4	0	0	2 (<0.1)	0
Pain	--	--	--	--
Any (Grade ≥1)	6277 (34.2)	1014 (11.1)	10326 (56.4)	1155 (13.0)
Grade 3	55 (0.3)	3 (<0.1)	301 (1.6)	7 (<0.1)
Grade 4	0	0	1 (<0.1)	0
Tenderness	--	--	--	--
Any (Grade ≥1)	9568 (52.2)	1527 (16.8)	12716 (69.4)	1329 (14.9)
Grade 3	156 (0.9)	18 (0.2)	844 (4.6)	18 (0.2)
Grade 4	0	0	2 (<0.1)	0
Pain/tenderness	--	--	--	--
Any (Grade ≥1)	10574 (57.7)	1907 (20.9)	13637 (74.4)	1806 (20.3)
Grade 3	189 (1.0)	20 (0.2)	1005 (5.5)	22 (0.2)
Grade 4	0	0	2 (<0.1)	0
Erythema (redness)	--	--	--	--
Any (Grade ≥1)	165 (0.9)	28 (0.3)	1142 (6.2)	30 (0.3)
Grade 3	2 (<0.1)	0	126 (0.7)	2 (<0.1)
Grade 4	0	0	0	0

Event	Original Monovalent Dose 1 N=18334 n (%)	Placebo Dose 1 N=9106 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Placebo Dose 2 N=8916 n (%)
Swelling	--	--	--	--
Any (Grade ≥1)	153 (0.8)	25 (0.3)	1061 (5.8)	26 (0.3)
Grade 3	4 (<0.1))	1 (<0.1)	72 (0.4)	1 (<0.1)
Grade 4	0	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 40, Page 92-93
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the Daily Illness Symptoms Diary within 7 days of the dose;
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The overall percentages of participants who experienced any solicited local injection site TEAE were higher for the Original Monovalent group at 57.9% compared with 21.2 % for the placebo group for Dose 1 and 74.6% for the Dose 2 Original Monovalent group compared with 20.5% in the Dose 2 placebo group. The most common solicited local injection site TEAEs were pain and/ or tenderness for both Dose 1 and Dose 2. Generally, solicited local injection site TEAEs increased between Dose 1 and Dose 2, and Grade 4 reactions were seen after the second dose.

As shown in the table below, the overall frequencies and percentages of participants 18 to <65 years of age who experienced any solicited local injection site TEAE were higher for the Original Monovalent group at 60.7% compared with 21.9% for the placebo group for Dose 1 and 81.1% for the Dose 2 Original Monovalent group compared with 22.3% in the Dose 2 placebo group. The most common solicited local injection site TEAE was Pain and/or Tenderness for both Dose 1 and Dose 2. As with the Overall Safety Analysis Set, solicited local injection site TEAEs increased between Dose 1 and Dose 2, and Grade 4 reactions were seen after the second dose.

Table 13. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Each Dose of the Initial Vaccination Period in Participants 18 to <65 Years of Age, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=16041 n (%)	Placebo Dose 1 N=7968 n (%)	Original Monovalent Dose 2 N=16106 n (%)	Placebo Dose 2 N=7859 n (%)
Any solicited local injection site TEAE	--	--	--	--
Any (Grade ≥1)	9728 (60.6)	1744 (21.9)	12382 (76.9)	1658 (21.1)
Grade 3	181 (1.1)	18 (0.2)	1081 (6.7)	22 (0.3)
Grade 4	0	0	2 (<0.1)	0
Pain	--	--	--	--
Any (Grade ≥1)	5816 (36.3)	921 (11.6)	9436 (58.6)	1041 (13.2)
Grade 3	52 (0.3)	2 (<0.1)	287 (1.8)	6 (<0.1)
Grade 4	0	0	1 (<0.1)	0
Tenderness	--	--	--	--
Any (Grade ≥1)	8796 (54.8)	1379 (17.3)	11543 (71.7)	1221 (15.5)
Grade 3	146 (0.9)	16 (0.2)	811 (5.0)	17 (0.2)
Grade 4	0	0	2 (<0.1)	0

Event	Original Monovalent Dose 1 N=16041 n (%)	Placebo Dose 1 N=7968 n (%)	Original Monovalent Dose 2 N=16106 n (%)	Placebo Dose 2 N=7859 n (%)
Pain/tenderness	--	--	--	--
Any (Grade ≥1)	9701 (60.5)	1728 (21.7)	12356 (76.7)	1644 (20.9)
Grade 3	176 (1.1)	17 (0.2)	962 (6.0)	20 (0.3)
Grade 4	0	0	2 (<0.1)	0
Erythema (redness)	--	--	--	--
Any (Grade ≥1)	148 (0.9)	23 (0.3)	1039 (6.5)	26 (0.3)
Grade 3	2 (<0.1)	0	119 (0.7)	2 (<0.1)
Grade 4	0	0	0	0
Swelling	--	--	--	--
Any (Grade ≥1)	136 (0.8)	23 (0.3)	945 (5.9)	22 (0.3)
Grade 3	4 (<0.1)	1 (<0.1)	67 (0.4)	1 (<0.1)
Grade 4	0	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 42, Page 96
Abbreviations: FDA=U.S. Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose of interest and completed at least 1 day of the reactogenicity diary for that dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities.

As presented in the table below, the overall frequency and percentages of participants 65 years of age and older who experienced any solicited local injection site TEAE was lower compared with the 18 to <65 years of age group (Original Monovalent group 38.4% versus 16.0% for the placebo group for Dose 1 and 61.9% for the Dose 2 Original Monovalent group versus 16.7% in the Dose 2 placebo group). The most common solicited local injection site TEAE was Pain/Tenderness for both Dose 1 and Dose 2. As with the Overall Safety Analysis Set, solicited local injection site TEAEs increased between Dose 1 and Dose 2; however, Grade 4 reactions after the second dose were not seen.

Table 14. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Each Dose of the Initial Vaccination Period in Participants ≥65 Years of Age, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=2293 n (%)	Placebo Dose 1 N=1138 n (%)	Original Monovalent Dose 2 N=2217 n (%)	Placebo Dose 2 N=1057 n (%)
Any solicited local injection site TEAE	--	--	--	--
Any (Grade ≥1)	880 (38.4)	182 (16.0)	1286 (58.0)	166 (15.7)
Grade 3	13 (0.6)	3 (0.3)	53 (2.4)	2 (0.2)
Grade 4	0	0	0	0
Pain	--	--	--	--
Any (Grade ≥1)	461 (20.1)	93 (8.2)	890 (40.1)	114 (10.8)
Grade 3	3 (0.1)	1 (<0.1)	14 (0.6)	1 (<0.1)
Grade 4	0	0	0	0
Tenderness	--	--	--	--
Any (Grade ≥1)	772 (33.7)	148 (13.0)	1173 (52.9)	108 (10.2)
Grade 3	10 (0.4)	2 (0.2)	33 (1.5)	1 (<0.1)
Grade 4	0	0	0	0

Event	Original Monovalent Dose 1 N=2293 n (%)	Placebo Dose 1 N=1138 n (%)	Original Monovalent Dose 2 N=2217 n (%)	Placebo Dose 2 N=1057 n (%)
Pain/tenderness	--	--	--	--
Any (Grade ≥1)	873 (38.1)	179 (15.7)	1281 (57.8)	162 (15.3)
Grade 3	13 (0.6)	3 (0.3)	43 (1.9)	2 (0.2)
Grade 4	0	0	0	0
Erythema (redness)	--	--	--	--
Any (Grade ≥1)	17 (0.7)	5 (0.4)	103 (4.6)	4 (0.4)
Grade 3	0	0	7 (0.3)	0
Grade 4	0	0	0	0
Swelling	--	--	--	--
Any (Grade ≥1)	17 (0.7)	2 (0.2)	116 (5.2)	4 (0.4)
Grade 3	0	0	5 (0.2)	0
Grade 4	0	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 43, Page 98
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose of interest and completed at least 1 day of the reactogenicity diary for that dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

As presented in the table below, the median day of onset for any solicited local TEAE was 2 days for both Dose 1 and Dose 2 for participants in the Safety Analysis Set who received the Original monovalent vaccine. Most of the individual solicited local TEAEs had a 2-day median onset except for redness which had a median onset of 3 days after Dose 2. In general, the number of events that persisted beyond 7 days was higher after the second dose for any solicited local TEAE.

Table 15. Characteristics of Solicited Local TEAEs in the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=18334	Placebo Dose 1 N=9106	Original Monovalent Dose 2 N=18323	Placebo Dose 2 N=8916
Any solicited local TEAE	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	2 (1, 7)	2 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	3 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	8	2	26	2
Pain	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	2 (1, 7)	2 (1, 7)	2 (1, 7)
Duration within period: median (min, max)	1 (1, 7)	1 (1, 7)	2 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	1	1	5	1
Tenderness	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	2 (1, 7)	2 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	3 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	5	2	16	1
Pain/tenderness	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	2 (1, 7)	2 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	3 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	6	2	18	2

Event	Original Monovalent Dose 1 N=18334	Placebo Dose 1 N=9106	Original Monovalent Dose 2 N=18323	Placebo Dose 2 N=8916
Redness (erythema)	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	2 (1, 7)	3 (1, 7)	2 (1, 7)
Duration within period: median (min, max)	1 (1, 7)	1 (1, 5)	2 (1, 7)	1 (1, 6)
Persisted beyond 7 days[a]	1	0	8	1
Swelling	--	--	--	--
Day of onset: median (min, max)	2 (1, 7)	1 (1, 7)	2 (1, 7)	2 (1, 7)
Duration within period: median (min, max)	1 (1, 7)	1 (1, 6)	2 (1, 7)	1 (1, 5)
Persisted beyond 7 days	1	0	5	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 41, Page 94
Abbreviations: max=maximum; min=minimum; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the first vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose; NVX-CoV2373=5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant.
a. Events reported on the Adverse Events CRF with a start date within 8 days of the relevant dosing date, an end date 8 or more days from the relevant dosing date and were mapped to a reactogenicity term

The subgroup analyses for Dose 1 and 2 Solicited Local Injection Site TEAEs (Age, Sex, Race, Ethnicity, Country, Co-morbidities, and High-Risk Status) demonstrated the following trends[2]:

- The percentages of events were lower in the >65 years of age group compared with the 18 through 65 years of age group (discussed above).
- The percentages of events were higher in females (Male: Dose 1, 53.3%; Dose 2, 69.9% versus Female: Dose 1, 62.9%; Dose 2, 79.6%).
- The percentages Black or African Americans who experienced events were lower compared with the other ethnic subgroups (Dose 1, 43.0% compared with 60 - 65.8% for other races; Dose 2, 56.7% compared with 67.0% -82.8% for other races). For Ethnicity, the proportion of events were similar.
- There was a higher percentage of events in participants from the Mexico (Dose 1, 68.6%, Dose 2, 83.9%) compared with participants from the U.S. (Dose 1, 68.6, Dose 2, 83.9).
- The percentages of events in chronic lung disease were slightly higher compared with the other co-morbidity subgroups (Dose 1, 58.2% compared with 39.8 - 49.0% for the other co-morbidities; Dose 2, 78.1% compared with 58.4% - 71.6% for the other co-morbidities).
- The percentages of events between participants with high-risk and not high-risk status were similar.
- The subgroups with the highest percentage of ≥Grade 3 reactions with 2 doses of vaccine are participants from Mexico (Dose 2, 10.1%), Multiple (Dose 2, 9.2%), and Females (Dose 2, 8.4%)

2 Protocol 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 44, Page 100

The frequency and percentage of adult participants reporting solicited local injection site TEAEs within 7 Days after primary (Safety Analysis Set) and booster (Booster Safety Analysis Set) vaccination of Original Monovalent are presented in the table below.

Table 16. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Primary, Safety Analysis Set, and Booster, Booster Safety Analysis Set, Vaccination of Original Monovalent, Adult Main Study 301

Event	Original Monovalent Dose 1 N=18334 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Original Monovalent Booster N=11447 n (%)
Any solicited local injection site TEAE	--	--	--
Any (Grade ≥1)	10608 (57.9)	13668 (74.6)	8332 (72.8)
Grade 3	194 (1.1)	1134 (6.2)	1014 (8.9)
Grade 4	0	2 (<0.1)	9 (<0.1)
Pain	--	--	--
Any (Grade ≥1)	6277 (34.2)	10326 (56.4)	6453 (56.4)
Grade 3	55 (0.3)	301 (1.6)	313 (2.7)
Grade 4	0	1 (<0.1)	6 (<0.1)
Tenderness	--	--	--
Any (Grade ≥1)	9568 (52.2)	12716 (69.4)	7698 (67.2)
Grade 3	156 (0.9)	844 (4.6)	711 (6.2)
Grade 4	0	2 (<0.1)	7 (<0.1)
Pain/tenderness	--	--	--
Any (Grade ≥1)	10574 (57.7)	13637 (74.4)	8293 (72.4)
Grade 3	189 (1.0)	1005 (5.5)	859 (7.5)
Grade 4	0	2 (<0.1)	9 (<0.1)
Erythema (redness)	--	--	--
Any (Grade ≥1)	165 (0.9)	1142 (6.2)	953 (8.3)
Grade 3	2 (<0.1)	126 (0.7)	183 (1.6)
Grade 4	0	0	0
Swelling	--	--	--
Any (Grade ≥1)	153 (0.8)	1061 (5.8)	873 (7.6)
Grade 3	4 (<0.1)	72 (0.4)	109 (1.0)
Grade 4	0	0	0

Source: Table 19 Page 43, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

Local solicited adverse reactions increased after Dose 2 of Original Monovalent and remained elevated after the third dose. There were higher percentages of participants who experienced Erythema (redness) and Swelling after Dose 3 of Original Monovalent compared with Dose 2 (8.3% vs. 6.2% and 7.6% vs. 5.8% respectively); however, a lower overall percentages of participants reported a solicited adverse event after Dose 3 (72.8%) compared with Dose 2 (74.6%). The overall percentage of participants who reported Grade 3 local solicited adverse events increased with subsequent doses (1.1%, 6.2%, and 8.9% respectively). There were 2 (<0.1) participants reporting Grade 4 local solicited adverse events after Dose 2, and 9 (<0.1) participants who reported Grade 4 local solicited adverse events after Dose 3.

The subgroup analyses of Dose 3 Solicited Local Injection Site TEAEs (Age, Sex, Race, Ethnicity, Country, Co-morbidities, and High-Risk Status) demonstrated the following trends[3]:

- The percentages of events were lower in the >65 years of age group compared with the 18 to 65 years of age group (59.8% versus 75.0% respectively).
- The percentages of events were higher in females (Male 67.4% versus Female 78.1%).
- The percentages of Native Hawaiian or Other Pacific Islander who experienced events were lower compared with the other ethnic subgroups (57.1% compared with 62.4 - 79.3% for other races,). For Ethnicity, the proportion of events were similar.
- There was a higher percentage of events in participants from the Mexico (86.8%) compared with participants from the U.S. (78.5%).
- The percentages of events in chronic lung disease were slightly higher compared with the other co-morbidity subgroups (78.9% compared with 66.2% - 78.9% for the other co-morbidities).
- The percentages of events between participants with high-risk status and not high-risk status were similar.
- The subgroups with the highest percentage of ≥Grade 3 reactions with 2 doses of vaccine are participants from Multiple (13.1%), Mexico (12.9%), and Females (11.7%).

Solicited Systemic Events

The frequency and percentage of solicited systemic TEAEs within 7 days after each dose of the initial vaccination period by maximum severity in the Safety Analysis Set is presented in the table below.

Table 17. Frequency and Percentage of Solicited Systemic TEAEs Within 7 Days After Each Dose of the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=18334 n (%)	Placebo Dose 1 N=9106 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Placebo Dose 2 N=8916 n (%)
Any solicited systemic TEAE	--	--	--	--
Any (Grade ≥1)	8835 (48.2)	3713 (40.8)	12646 (69.0)	3162 (35.5)
Grade 3	646 (3.5)	296 (3.3)	3137 (17.1)	391 (4.4)
Grade 4	16 (<0.1)	6 (<0.1)	12 (<0.1)	7 (<0.1)
Fever	--	--	--	--
Any (Grade ≥1)	70 (0.4)	37 (0.4)	1107 (6.0)	29 (0.3)
Grade 3	9 (<0.1)	7 (<0.1)	81 (0.4)	6 (<0.1)
Grade 4	7 (<0.1)	3 (<0.1)	2 (<0.1)	2 (<0.1)
Headache	--	--	--	--
Any (Grade ≥1)	4674 (25.5)	2141 (23.5)	8181 (44.6)	1757 (19.7)
Grade 3	146 (0.8)	62 (0.7)	518 (2.8)	38 (0.4)
Grade 4	4 (<0.1)	1 (<0.1)	3 (<0.1)	2 (<0.1)

3 Protocol 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 54, Page 127-128

Fatigue	--	--	--	--
Any (Grade ≥1)	4774 (26.0)	2090 (23.0)	8780 (47.9)	1886 (21.2)
Grade 3	464 (2.5)	217 (2.4)	2660 (14.5)	341 (3.8)
Grade 4	3 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Malaise	--	--	--	--
Any (Grade ≥1)	2690 (14.7)	1063 (11.7)	6742 (36.8)	1038 (11.6)
Grade 3	138 (0.8)	56 (0.6)	1083 (5.9)	59 (0.7)
Grade 4	6 (<0.1)	1 (<0.1)	5 (<0.1)	2 (<0.1)
Fatigue/malaise	--	--	--	--
Any (Grade ≥1)	5488 (29.9)	2384 (26.2)	9856 (53.8)	2128 (23.9)
Grade 3	509 (2.8)	230 (2.5)	2829 (15.4)	354 (4.0)
Grade 4	7 (<0.1)	1 (<0.1)	5 (<0.1)	3 (<0.1)
Muscle pain (myalgia)	--	--	--	--
Any (Grade ≥1)	4273 (23.3)	1286 (14.1)	9318 (49.9)	1125 (12.6)
Grade 3	82 (0.4)	35 (0.4)	850 (4.6)	30 (0.3)
Grade 4	2 (<0.1)	1 (<0.1)	2 (<0.1)	4 (<0.1)
Joint pain (arthralgia)	--	--	--	--
Any (Grade ≥1)	1413 (7.7)	600 (6.6)	3856 (21.0)	577 (6.5)
Grade 3	53 (0.3)	29 (0.3)	419 (2.3)	24 (0.3)
Grade 4	1 (<0.1)	0	2 (<0.1)	2 (<0.1)
Nausea/vomiting	--	--	--	--
Any (Grade ≥1)	1270 (6.9)	560 (6.1)	2085 (11.4)	482 (5.4)
Grade 3	18 (<0.1)	7 (<0.1)	31 (0.2)	7 (<0.1)
Grade 4	4 (<0.1)	2 (<0.1)	5 (<0.1)	2 (<0.1)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Table 16, Page 37-38
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The overall percentages of participants who experienced any solicited systemic TEAE for the Original Monovalent group was 48.2% compared with 40.8 % for the placebo group for Dose 1 and 69.0% for the Dose 2 Original Monovalent group compared with 35.5% in the Dose 2 placebo group. The most common solicited systemic TEAEs were fatigue, malaise, headache, and muscle pain (myalgia) for Dose 1 and Dose 2. Generally, solicited systemic TEAEs increased between Dose 1 and Dose 2, and Grade 4 reactions were seen after both doses.

Grade 3 and 4 solicited systemic ARs were reported by 3.5% and <0.1% of participants, respectively, post-Dose 1 and by 17.1% and <0.1% of participants, respectively, post-Dose 2.

The frequency and percentage of solicited systemic TEAEs within 7 days after each dose of the initial vaccination period in the subset of participants 18 to <65 years of age by maximum severity in the Safety Analysis Set are presented in the table below.

Table 18. Frequency and Percentage of Solicited Systemic TEAEs Within 7 Days After Each Dose of the Initial Vaccination Period in Participants 18 to <65 Years of Age, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=16041 n (%)	Placebo Dose 1 N=7968 n (%)	Original Monovalent Dose 2 N=16106 n (%)	Placebo Dose 2 N=7859 n (%)
Any solicited systemic TEAE	--	--	--	--
Any (Grade ≥1)	8052 (50.2)	3339 (41.9)	11561 (71.8)	2864 (36.4)
Grade 3	562 (3.5)	263 (3.3)	2981 (18.5)	354 (4.5)
Grade 4	16 (<0.1)	4 (<0.1)	11 (<0.1)	7 (<0.1)
Fever	--	--	--	--
Any (Grade ≥1)	61 (0.4)	31 (0.4)	1062 (6.6)	22 (0.3)
Grade 3	8 (<0.1)	7 (<0.1)	79 (0.5)	5 (<0.1)
Grade 4	7 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Headache	--	--	--	--
Any (Grade ≥1)	4292 (26.8)	1942 (24.4)	7630 (47.4)	1596 (20.3)
Grade 3	134 (0.8)	58 (0.7)	500 (3.1)	36 (0.5)
Grade 4	4 (<0.1)	1 (<0.1)	2 (<0.1)	2 (<0.1)
Fatigue	--	--	--	--
Any (Grade ≥1)	4343 (27.1)	1894 (23.8)	8133 (50.5)	1723 (21.9)
Grade 3	391 (2.4)	190 (2.4)	2522 (15.7)	307 (3.9)
Grade 4	3 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)
Malaise	--	--	--	--
Any (Grade ≥1)	2460 (15.3)	963 (12.1)	6273 (38.9)	943 (12.0)
Grade 3	126 (0.8)	52 (0.7)	1043 (6.5)	54 (0.7)
Grade 4	6 (<0.1)	1 (<0.1)	5 (<0.1)	2 (<0.1)
Fatigue/malaise	--	--	--	--
Any (Grade ≥1)	4999 (31.2)	2157 (27.1)	9108 (56.6)	1940 (24.7)
Grade 3	433 (2.7)	203 (2.5)	2687 (16.7)	319 (4.1)
Grade 4	7 (<0.1)	1 (<0.1)	5 (<0.1)	3 (<0.1)
Muscle pain (myalgia)	--	--	--	--
Any (Grade ≥1)	3949 (24.6)	1142 (14.3)	8490 (52.7)	1010 (12.9)
Grade 3	79 (0.5)	31 (0.4)	818 (5.1)	28 (0.4)
Grade 4	2 (<0.1)	1 (<0.1)	2 (<0.1)	4 (<0.1)
Joint pain (arthralgia)	--	--	--	--
Any (Grade ≥1)	1272 (7.9)	528 (6.6)	3574 (22.2)	514 (6.5)
Grade 3	49 (0.3)	25 (0.3)	403 (2.5)	22 (0.3)
Grade 4	1 (<0.1)	0	2 (<0.1)	2 (<0.1)
Nausea/vomiting	--	--	--	--
Any (Grade ≥1)	1150 (7.2)	513 (6.4)	1953 (12.1)	443 (5.6)
Grade 3	18 (0.1)	7 (<0.1)	29 (0.2)	7 (<0.1)
Grade 4	4 (<0.1)	2 (<0.1)	5 (<0.1)	2 (<0.1)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Table 17, Page 39
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The overall percentages of participants 18 through 64 years of age who experienced any solicited systemic TEAE for the Original Monovalent group was 50.2% compared with 41.9% for

the placebo group for Dose 1 and 71.8% for the Dose 2 Original Monovalent group compared with 36.4% in the Dose 2 placebo group. The most common solicited systemic TEAEs were fatigue, malaise, headache, and muscle pain (myalgia) for Dose 1 and Dose 2. As with the overall Safety Analysis Set, solicited systemic TEAEs increased between Dose 1 and Dose 2, and Grade 4 reactions were seen after both doses.

The frequency and percentage of solicited systemic TEAEs within 7 days after each dose of the initial vaccination period in the subset of participant ≥65 years of age by maximum severity in the Safety Analysis Set is presented in the table below.

Table 19. Frequency and Percentage of Solicited Systemic TEAEs Within 7 Days After Each Dose of the Initial Vaccination Period in Participants ≥65 Years of Age, Safety Analysis Set, Adult Main Study 301

Event	Original Monovalent Dose 1 N=2293 n (%)	Placebo Dose 1 N=1138 n (%)	Original Monovalent Dose 2 N=2217 n (%)	Placebo Dose 2 N=1057 n (%)
Any solicited systemic TEAE	--	--	--	--
Any (Grade ≥1)	783 (34.1)	374 (32.9)	1085 (48.9)	298 (28.2)
Grade 3	84 (3.7)	33 (2.9)	156 (7.0)	37 (3.5)
Grade 4	0	~~0~~2 (0.2)	1 (<0.1)	0
Fever	--	--	--	--
Any (Grade ≥1)	9 (0.4)	6 (0.5)	45 (2.0)	7 (0.7)
Grade 3	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Grade 4	0	~~0~~2 (0.2)	0	0
Headache	--	--	--	--
Any (Grade ≥1)	382 (16.7)	199 (17.5)	551 (24.9)	161 (15.2)
Grade 3	12 (0.5)	4 (0.4)	18 (0.8)	2 (0.2)
Grade 4	0	0	1 (<0.1)	0
Fatigue	--	--	--	--
Any (Grade ≥1)	431 (18.8)	196 (17.2)	647 (29.2)	163 (15.4)
Grade 3	73 (3.2)	27 (2.4)	138 (6.2)	34 (3.2)
Grade 4	0	0	0	0
Malaise	--	--	--	--
Any (Grade ≥1)	230 (10.0)	100 (8.8)	469 (21.2)	95 (9.0)
Grade 3	12 (0.5)	4 (0.4)	40 (1.8)	5 (0.5)
Grade 4	0	0	0	0
Fatigue/malaise	–	–	–	–
Any (Grade ≥1)	489 (21.3)	227 (19.9)	748 (33.7)	188 (17.8)
Grade 3	76 (3.3)	27 (2.4)	142 (6.4)	35 (3.3)
Grade 4	0	0	0	0
Muscle pain (myalgia)	--	--	--	--
Any (Grade ≥1)	324 (14.1)	144 (12.7)	648 (29.2)	115 (10.9)
Grade 3	3 (0.1)	4 (0.4)	32 (1.4)	2 (0.2)
Grade 4	0	0	0	0
Joint pain (arthralgia)	--	--	--	--
Any (Grade ≥1)	141 (6.1)	72 (6.3)	282 (12.7)	63 (6.0)
Grade 3	4 (0.2)	4 (0.4)	16 (0.7)	2 (0.2)
Grade 4	0	0	0	0

Event	Original Monovalent Dose 1 N=2293 n (%)	Placebo Dose 1 N=1138 n (%)	Original Monovalent Dose 2 N=2217 n (%)	Placebo Dose 2 N=1057 n (%)
Nausea/vomiting	--	--	--	--
Any (Grade ≥1)	120 (5.2)	47 (4.1)	132 (6.0)	39 (3.7)
Grade 3	0	0	2 (<0.1)	0
Grade 4	0	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR Table 48, Pages 112-113
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The overall percentages of participants who experienced any solicited systemic TEAE for the Original Monovalent group was 34.1% compared with 32.9% for the placebo group for Dose 1 and 48.9% for the Dose 2 Original Monovalent group compared with 28.2% in the Dose 2 placebo group. The most common solicited systemic TEAEs were fatigue, malaise, headache, and muscle pain (myalgia) for Dose 1 and Dose 2. As with the overall Safety Analysis Set, solicited systemic injection site TEAEs increased between Dose 1 and Dose 2. Grade 4 reactions were not seen in the vaccine group in subjects aged ≥65 years; however, two Grade 4 reactions [(fever 2 (0.2%)] were noted after Dose 1 of placebo.

The subgroup analysis for Dose 1 and 2 Solicited Systemic Injection Site TEAEs (Age, Sex, Race, Ethnicity, Country, Co-morbidities, and High-Risk Status) demonstrated the following trends[4]:

- The percentages of events were lower in the >65 years of age group compared with the 18 to 65 years of age group (discussed above).
- The percentages of events were higher in females (Male: Dose 1, 43.2%; Dose 2, 64.7% versus Female: Dose 1, 53.7%; Dose 2, 73.7%).
- The percentages Black or African Americans who experienced events were lower compared with the other ethnic subgroups (Dose 1, 41.0% compared with 48.7% – 56.1% for other races; Dose 2, 48.4% compared with 67.2% - 80.1% for other races). For Ethnicity, the percentage of events were similar.
- There was a higher percentage of events in participants from the Mexico (Dose 1, 53.6%, Dose 2, 73.4%) compared with participants from the U.S. (Dose 1, 47.3%, Dose 2, 69.2%).
- The percentages of events in chronic lung disease were slightly higher compared with the other co-morbidity subgroups (Dose 1, 53.2% compared with 35.2 – 45.9% for the other co-morbidities; Dose 2, 69.3% compared with 46.2% - 61.3% for the other co-morbidities).
- The percentages of events between participants with high-risk and not high-risk status

[4] Protocol 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 49, Page 115-118

were similar.

- The subgroups with the highest percentage of ≥Grade 3 reactions with 2 doses of vaccine are participants from Multiple (Dose 2, 23.9%), Native Hawaiian or Other Pacific Islander (Dose 2, 22.9%), and Asian (Dose 2, 22.8%)
- Solicited systemic TEAEs were comparable or higher in the vaccine group compared with the placebo group.

The frequency and percentage of adult participants reporting solicited systemic TEAEs within 7 Days after primary (Safety Analysis Set) and booster (Booster Safety Analysis Set) vaccination of Original Monovalent are presented in the table below.

Table 20. Frequency and Percentage of Solicited Systemic TEAEs Within 7 Days After Primary, Safety Analysis Set, and Booster, Booster Safety Analysis Set, Vaccination of Original Monovalent, Adult Main Study 301

Event	Original Monovalent Dose 1 N=18334 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Original Monovalent Booster N=11447 n (%)
Any solicited systemic TEAE	--	--	--
Any (Grade ≥1)	8835 (48.2)	12646 (69.0)	7954 (69.5)
Grade 3	646 (3.5)	3137 (17.1)	2372 (20.7)
Grade 4	16 (<0.1)	12 (<0.1)	24 (0.2)
Fever	--	--	--
Any (Grade ≥1)	70 (0.4)	1107 (6.0)	929 (8.1)
Grade 3	9 (<0.1)	81 (0.4)	126 (1.1)
Grade 4	7 (<0.1)	2 (<0.1)	6 (<0.1)
Headache	--	--	--
Any (Grade ≥1)	4674 (25.5)	8181 (44.6)	5071 (44.3)
Grade 3	146 (0.8)	518 (2.8)	569 (5.0)
Grade 4	4 (<0.1)	3 (<0.1)	6 (<0.1)
Fatigue	--	--	--
Any (Grade ≥1)	4774 (26.0)	8780 (47.9)	5708 (49.9)
Grade 3	464 (2.5)	2660 (14.5)	1969 (17.2)
Grade 4	3 (<0.1)	2 (<0.1)	12 (0.1)
Malaise	--	--	--
Any (Grade ≥1)	2690 (14.7)	6742 (36.8)	4312 (37.7)
Grade 3	138 (0.8)	1083 (5.9)	985 (8.6)
Grade 4	6 (<0.1)	5 (<0.1)	12 (0.1)
Fatigue/malaise	--	--	--
Any (Grade ≥1)	5488 (29.9)	9856 (53.8)	6323 (55.2)
Grade 3	509 (2.8)	2829 (15.4)	2102 (18.4)
Grade 4	7 (<0.1)	5 (<0.1)	13 (0.1)
Muscle pain (myalgia)	--	--	--
Any (Grade ≥1)	4273 (23.3)	9138 (49.9)	5852 (51.1)
Grade 3	82 (0.4)	850 (4.6)	893 (7.8)
Grade 4	2 (<0.1)	2 (<0.1)	11 (<0.1)
Joint pain (arthralgia)	--	--	--
Any (Grade ≥1)	1413 (7.7)	3856 (21.0)	2768 (24.2)
Grade 3	53 (0.3)	419 (2.3)	522 (4.6)
Grade 4	1 (<0.1)	2 (<0.1)	6 (<0.1)

Event	Original Monovalent Dose 1 N=18334 n (%)	Original Monovalent Dose 2 N=18323 n (%)	Original Monovalent Booster N=11447 n (%)
Nausea/vomiting	--	--	--
Any (Grade ≥1)	1270 (6.9)	2085 (11.4)	1330 (11.6)
Grade 3	18 (<0.1)	31 (0.2)	47 (0.4)
Grade 4	4 (<0.1)	5 (<0.1)	5 (<0.1)

Source: Table 22 Page 47, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the Daily Illness Symptoms Diary that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperate in the Daily Illness Symptoms Diary within 7 days of the dose
Note: At each level of summarization, a participant is counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period is summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

There was a strong overall trend towards increasing percentages of participants reporting systemic solicited adverse reactions with subsequent vaccine doses (48.2% after Dose 1, 69.0% after Dose 2, and 69.5% after Dose 3, respectively). The overall percentage of participants who reported Grade 3 local solicited adverse events also increased with subsequent doses (646 [3.5%], 3,137 [17.1%], and 2,372 [20.7%], respectively). Participants reported Grade 4 local solicited adverse events after all three doses (16 [<0.1%], 12 [<0.1%], and 24 [0.2%], respectively).

> *Reviewer Comment: There is a trend towards increasing solicited adverse events with subsequent vaccine doses, particularly systemic solicited events. Grade 4 adverse events are noted after each vaccine dose. Roughly 70% of adults experienced a systemic solicited adverse event after three vaccine doses, and Grade 3 and 4 events were noted after each dose.*

The subgroup analysis of Dose 3 Solicited Local Injection Site TEAEs (Age, Sex, Race, Ethnicity, Country, Co-morbidities, and High-Risk Status) demonstrated the following trends[5]:

- The percentages of events were lower in the >65 years of age group compared with the 18 through 65 years of age group (53.1% versus 72.2%, respectively).
- The percentages of events were higher in females (Male 64.8% versus Female 74.1%).
- The percentages Asian who experienced events were lower compared with the other ethnic subgroups (77.4% compared with 64.9– 75.3% for other races). For Ethnicity, the percentage of events were similar.
- There was a higher percentage of events in participants from Mexico (76.9 %) compared with participants from the U.S. (71.8 %).
- The percentages of events in chronic lung disease were slightly higher compared with the other co-morbidity subgroups (71.8% compared with 46.9% - 66.8% for the other co-morbidities).
- The percentages of events between participants with high-risk status and not high-risk

[5] Protocol 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 59, Page 138-139

status were similar.

- The subgroups with the highest percentage of ≥Grade 3 reactions with the Booster of vaccine are participants from Asian (22.6%), White and Not Reported (Race) (22.5%), and Hispanic or Latino (22.1%).

Clinical Reviewer Comment: In summary, subgroup analyses demonstrate that roughly half of vaccinated participants experienced either local or systemic solicited adverse reactions after the first vaccine dose, and there was a trend towards increasing numbers of adverse events with subsequent vaccine doses, with approximately 70 percent of vaccinated participants experiencing both local and systemic solicited adverse events after the third dose. Grade 4 local and systemic adverse events were seen in this study, and there was a trend towards increasing percentages of Grade 3 and Grade 4 adverse events with subsequent doses.

Unsolicited Adverse Events

Unsolicited adverse events through the cutoff date of August 18, 2022, are presented in this section. The tables were updated based on dataset reformatting that was recommended by the Division. Specifically, these analyses now include the data from the COVID-19 Symptom Daily Diary. Once included, these data substantially increased the number unsolicited adverse events for each treatment period compared with earlier analyses of unsolicited adverse events which did not include data from the COVID-19 Symptoms Daily Diary. This review will not attempt to explain or analyze the differences between the current unsolicited adverse event safety data and the data from previous data submissions.

Unsolicited Adverse Events (Pre-Crossover)

A summary of frequency and percentage of unsolicited adverse events during the Initial Vaccination Period for the safety analysis set are summarized in the table below.

Table 21. Frequency and Percentage of Unsolicited Adverse Events During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Participants Reporting at Least One	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Unsolicited TEAEs through 28 days after Dose 2	--	--
Unsolicited TEAE	6817 (34.5)	3423 (34.8)
Related unsolicited TEAE	476 (2.4)	141 (1.4)
Severe unsolicited TEAE	1049 (5.3)	562 (5.7)
Related severe unsolicited TEAE	19 (<0.1)	6 (<0.1)
MAAE	969 (4.9)	476 (4.8)
Unsolicited TEAEs through data cut-off date	--	--
Any MAAE	1097 (5.6)	530 (5.4)
Related MAAE	102 (0.5)	25 (0.3)
SAE	228 (1.2)	115 (1.2)
Related SAE	6 (<0.1)	3 (<0.1)
AESI (PIMMCs)	27 (0.1)	13 (0.1)
Related AESI (PIMMCs)	17 (<0.1)	3 (<0.1)
AESIs relevant to COVID-19	5 (<0.1)	6 (<0.1)
Related relevant to COVID-19	0	1 (<0.1)
Deaths	11 (<0.1)	7 (<0.1)
TEAE leading to discontinuation of the vaccine	60 (0.3)	21 (0.2)
Related TEAE leading to discontinuation of the vaccine	13 (<0.1)	3 (<0.1)

Participants Reporting at Least One	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
TEAE leading to study discontinuation	27 (0.1)	11 (0.1)
Related TEAE leading to study discontinuation	4 (<0.1)	2 (<0.1)

Source: Table 26 Page 54, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; PIMMC=potential immune-mediated medical condition; SAE=serious adverse event; TEAE=treatment emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.

Clinical Reviewer Comment: Overall, the percentages of participants who experienced unsolicited TEAEs were balanced between the two treatment groups (Original Monovalent 34.5% versus Placebo 34.8%). Similar balance was seen in the percentages of participants with related unsolicited TEAEs (Original Monovalent 2.4% versus Placebo 1.4%). In general, the percentages of participants who experienced MAAEs, AESI, SAEs, Deaths, and TEAEs leading to either study or vaccine discontinuation were low and similarly balanced.

The frequency and percentage of participants experiencing unsolicited adverse events, with an occurrence ≥0.1%, during the Initial Vaccination Period for the Safety Analysis Set, by system organ class and preferred term are presented in the table below.

Table 22. Frequency and Percentage of Unsolicited Adverse Events With Occurrence in ≥0.1% of Participants in the Original Monovalent Group During the Initial Vaccine Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Any TEAE within 28 days of second vaccination	6817 (34.5)	3423 (34.8)
Infections and infestations	473 (2.4)	246 (2.5)
Upper respiratory tract infection	72 (0.4)	34 (0.3)
Urinary tract infection	51 (0.3)	19 (0.2)
Viral infection	40 (0.2)	22 (0.2)
Sinusitis	31 (0.2)	22 (0.2)
Respiratory, thoracic, and mediastinal disorders	2924 (14.8)	1502 (15.3)
Nasal congestion	2237 (11.3)	1189 (12.1)
Rhinorrhea	2209 (11.2)	1187 (12.1)
Cough	956 (4.8)	508 (5.2)
Dyspnea	484 (2.5)	262 (2.7)
Oropharyngeal pain	58 (0.3)	29 (0.3)
Nervous system disorders	3147 (15.9)	1703 (17.3)
Headache	2974 (15.1)	1618 (16.4)
Anosmia	187 (0.9)	110 (1.1)
Ageusia	186 (0.9)	109 (1.1)
Dizziness	46 (0.2)	22 (0.2)
General disorders and administration site conditions	2200 (11.1)	1125 (11.4)
Pain	1139 (5.8)	632 (6.4)
Fatigue	956 (4.8)	521 (5.3)
Chills	630 (3.2)	312 (3.1)
Pyrexia	584 (3.0)	306 (3.1)
Injection site pruritus	21 (0.1)	0

System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Gastrointestinal disorders	1704 (8.6)	940 (9.5)
Diarrhea	1143 (5.8)	642 (6.5)
Nausea	750 (3.8)	400 (4.1)
Vomiting	740 (3.7)	390 (4.0)
Musculoskeletal and connective tissue disorders	1314 (6.7)	723 (7.3)
Myalgia	1149 (5.8)	633 (6.4)
Arthralgia	46 (0.2)	21 (0.2)
Back pain	37 (0.2)	24 (0.2)
Pain in extremity	22 (0.1)	12 (0.1)
Skin and subcutaneous tissue disorders	193 (1.0)	69 (0.7)
Rash	45 (0.2)	22 (0.2)
Pruritus	23 (0.1)	2 (<0.1)
Injury, poisoning, and procedural complications	193 (1.0)	97 (1.0)
Vascular disorders	114 (0.6)	57 (0.6)
Hypertension	75 (0.4)	47 (0.5)
Psychiatric disorders	110 (0.6)	49 (0.5)
Anxiety	35 (0.2)	15 (0.2)
Depression	22 (0.1)	10 (0.1)
Metabolism and nutrition disorders	78 (0.4)	46 (0.5)
Blood and lymphatic system disorders	77 (0.4)	20 (0.2)
Lymphadenopathy	49 (0.2)	11 (0.1)
Reproductive system and breast disorders	61 (0.3)	22 (0.2)
Eye disorders	55 (0.3)	15 (0.2)
Ear and labyrinth disorders	47 (0.2)	16 (0.2)
Investigations	46 (0.2)	14 (0.1)
Cardiac disorders	44 (0.2)	18 (0.2)
Immune system disorders	30 (0.2)	9 (<0.1)
Renal and urinary disorders	27 (0.1)	12 (0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	21 (0.1)	7 (<0.1)

Source: Table 32 Page 59, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; TEAE=treatment-emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
Note: Follow-up time is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment.

The percentage of participants who experienced any TEAE within 28 days of second vaccination (unsolicited adverse events) was balanced between the vaccine and placebo groups (Original Monovalent 34.5% vs Placebo 34.8%). There were no imbalances between the vaccine or placebo groups for any individual preferred term.

> *Clinical Reviewer Comment: There were no imbalances noted between the placebo and treatment groups for the percentages of participants who experienced any of the unsolicited adverse event preferred terms in the table above, hence no safety signal is present for overall unsolicited adverse events in the Safety Analysis Set.*

The frequency and percentage of participants experiencing unsolicited adverse events withing 28 days after receiving the second vaccination during the initial vaccination period for the Safety Analysis Set, by demographics and baseline characteristics are presented in the table below.

Table 23. Frequency and Percentage of Unsolicited Adverse Events Within 28 Days After the Second Vaccination During the Initial Vaccination Period by Demographic and Baseline Characteristics, Safety Analysis Set, Adult Main Study 301

Subgroup	Original Monovalent n/N (%)	Placebo n/N (%)
Age	--	--
Participants 18 to <65 years	6027/17255 (34.9)	3021/8612 (35.1)
Participants ≥65 years	790/2480 (31.9)	402/1235 (32.6)
Sex	--	--
Male	3101/10367 (29.9)	1500/5019 (29.9)
Female	3716/9368 (39.7)	1923/4828 (39.8)
Race	--	--
White	5206/14795 (35.2)	2600/7381 (35.2)
Black or African American	734/2322 (31.6)	394/1164 (33.8)
Asian	240/809 (29.7)	130/416 (31.3)
American Indian or Alaska Native	412/1309 (31.5)	205/660 (31.1)
Native Hawaiian or other Pacific Islander	20/56 (35.7)	5/12 (41.7)
Multiple	163/326 (50.0)	65/160 (40.6)
Not Reported	38/110 (34.5)	19/47 (40.4)
Ethnicity	--	--
Not Hispanic or Latino	5353/15346 (34.9)	2705/7669 (35.3)
Hispanic or Latino	1444/4333 (33.3)	713/2155 (33.1)
Country[a]	--	--
United States	2255/18559 (12.2)	1088/9259 (11.8)
Mexico	73/1176 (6.2)	36/588 (6.1)
Co-morbidities[a]	--	--
Obesity (BMI ≥30 kg/m^2)	934/7287 (12.8)	459/3667 (12.5)
Chronic lung disease	446/2796 (16.0)	229/1455 (15.7)
Chronic kidney disease	31/150 (20.7)	15/68 (22.1)
Cardiovascular disease	44/230 (19.1)	25/129 (19.4)
Diabetes mellitus type 2	208/1531 (13.6)	115/818 (14.1)
High risk status[a]	--	--
High risk	2241/18812 (11.9)	1084/9380 (11.6)
Not high risk	87/923 (9.4)	40/467 (8.6)

Source: Table 44 Page 84, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: BMI=body mass index; MedDRA=Medical Dictionary for Regulatory Activities; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; TEAE=treatment-emergent adverse event.; kg/m^2 – kilogram per square meter.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
Note: Follow-up time is defined as time from first dose to the earliest date of early termination, date of first crossover dose, date of death and date corresponding to the Day 49 assessment.
a. Subgroup analyses for country, co-morbidities, and high-risk status were not rerun using updated data.

The percentage of participants who experienced an unsolicited adverse event was higher in the treatment group compared with placebo (Original Monovalent 50.0% vs Placebo 40.6%) for “Multiple”, under Race. This percentage of participants was also slightly higher when compared with the other races, where the percentages ranged from 29.7% to 35.7%. The percentages of participants experiencing unsolicited adverse events were otherwise comparable between different racial groups studied, and there were no imbalances seen between the vaccine and placebo groups for each racial subgroup.

In the other subgroups that were analyzed during the Initial Vaccination Period, there were no imbalances between percentages of participants who experienced an unsolicited adverse event in the vaccine and placebo groups. In addition, subgroup analyses by age, ethnicity,

comorbidities, and high-risk status were comparable to each other. There were slightly higher percentages of female participants who experienced unsolicited adverse events compared with male participants (39.7% versus 29.9%), but the events were balanced between the vaccine and placebo groups. Overall, these data did not suggest any substantial differences in the safety profile of the prototype vaccine (Original Monovalent) in the above subgroups compared with the overall safety population.

Unsolicited Adverse Events (Post-Crossover)

A summary of frequency and percentage of unsolicited adverse events during the Post-Crossover Vaccination Period for the safety analysis set are summarized in the table below.

Table 24. Frequency and Percentage of Unsolicited Adverse Events During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Participants Reporting At Least One	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Unsolicited TEAEs through 28 days of second vaccination	--	--
Unsolicited TEAE	3088 (48.1)	3730 (24.4)
Related unsolicited TEAE	129 (2.0)	61 (0.4)
Severe unsolicited TEAE	1026 (16.0)	743 (4.9)
Related severe unsolicited TEAE	5 (<0.1)	3 (<0.1)
MAAE	269 (4.2)	555 (3.6)
Unsolicited TEAEs through data-cut date	--	--
Any MAAE	377 (5.9)	795 (5.2)
Related MAAE	26 (0.4)	29 (0.2)
SAE	164 (2.6)	364 (2.4)
Related SAE	2 (<0.1)	4 (<0.1)
AESI (PIMMCs)	13 (0.2)	19 (0.1)
Related AESI (PIMMCs)	7 (<0.1)	5 (<0.1)
AESIs relevant to COVID-19	5 (<0.1)	9 (<0.1)
Related relevant to COVID-19	0	0
Deaths	10 (0.2)	30 (0.2)
TEAE leading to discontinuation of the vaccine	3 (<0.1)	15 (<0.1)
Related TEAE leading to discontinuation of the vaccine	1 (<0.1)	2 (<0.1)
TEAE leading to study discontinuation	10 (0.2)	26 (0.2)

Source: Table 28 Pages 55-56, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; PIMMC=potential immune-mediated medical condition; SAE=serious adverse event TEAE=treatment emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.

Given the fact that all participants had received the vaccine during the Post-Crossover Vaccination Period, the absence of a placebo comparator group limits the conclusions that can be drawn. There were higher percentages of participants who experienced unsolicited TEAEs in the Placebo to Original Monovalent Group (48.1%) compared with the Original Monovalent to Placebo Group (24.4%). The percentage of participants with related unsolicited TEAEs in the Placebo to Original Monovalent Group was 2.0% versus 0.4% in the Original Monovalent to Placebo Group. The percentage of participants who reported severe unsolicited TEAEs in the Placebo to Original Monovalent Group was 16.0% versus 4.9% in the Original Monovalent to Placebo Group, and for related severe unsolicited TEAEs, the percentages were <0.1% for both groups.

In general, the percentages of participants who experienced MAAEs, AESI, SAEs, Deaths, and TEAEs leading to either study or vaccine discontinuation were and low and similarly balanced.

The frequency and percentage of participants experiencing unsolicited adverse events, with an occurrence >1%, during the Blinded Crossover Vaccination Period for the Safety Analysis Set, by system organ class and preferred term are presented in the table below.

Table 25. Frequency and Percentage of Unsolicited Adverse Events With Occurrence in ≥0.1% of Participants in the Placebo to Original Monovalent Group During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Any TEAE within 28 days of second vaccination	3088 (48.1)	3730 (24.4)
General disorders and administration site conditions	2173 (33.9)	1382 (9.0)
Pain	1642 (25.6)	737 (4.8)
Fatigue	1013 (15.8)	701 (4.6)
Pyrexia	740 (11.5)	404 (2.6)
Chills	731 (11.3)	401 (2.6)
Injection site pain	31 (0.5)	8 (<0.1)
Injection site erythema	11 (0.2)	2 (<0.1)
Injection site pruritus	9 (0.1)	0
Injection site swelling	8 (0.1)	0
Infections and infestations	100 (1.6)	227 (1.5)
Upper respiratory tract infection	21 (0.3)	42 (0.3)
Urinary tract infection	15 (0.2)	20 (0.1)
Viral infection	10 (0.2)	19 (0.1)
Sinusitis	7 (0.1)	19 (0.1)
Nervous system disorders	1717 (26.8)	1646 (10.8)
Headache	1688 (26.3)	1574 (10.3)
Ageusia	57 (0.9)	100 (0.7)
Anosmia	57 (0.9)	99 (0.6)
Respiratory, thoracic, and mediastinal disorders	979 (15.3)	1623 (10.6)
Nasal congestion	728 (11.3)	1220 (8.0)
Rhinorrhea	727 (11.3)	1219 (8.0)
Cough	363 (5.7)	661 (4.3)
Dyspnea	188 (2.9)	273 (1.8)
Oropharyngeal pain	10 (0.2)	33 (0.2)
Musculoskeletal and connective tissue disorders	1670 (26.0)	827 (5.4)
Myalgia	1642 (25.6)	738 (4.8)
Arthralgia	15 (0.2)	23 (0.2)
Pain in extremity	10 (0.2)	14 (<0.1)
Back pain	9 (0.1)	18 (0.1)
Gastrointestinal disorders	787 (12.3)	985 (6.4)
Diarrhea	472 (7.4)	656 (4.3)
Nausea	452 (7.0)	480 (3.1)
Vomiting	447 (7.0)	475 (3.1)
Injury, poisoning and procedural complications	45 (0.7)	85 (0.6)
Skin and subcutaneous tissue disorders	40 (0.6)	55 (0.4)
Rash	10 (0.2)	13 (<0.1)
Psychiatric disorder	25 (0.4)	36 (0.2)
Depression	11 (0.2)	11 (<0.1)

System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Metabolism and nutrition disorders	21 (0.3)	30 (0.2)
Vascular disorders	17 (0.3)	39 (0.3)
Hypertension	9 (0.1)	27 (0.2)
Investigations	11 (0.2)	23 (0.2)
Cardiac disorders	11 (0.2)	30 (0.2)
Reproductive system and breast disorders	11 (0.2)	21 (0.1)
Immune system disorders	10 (0.2)	17 (0.1)
Blood and lymphatic system disorders	10 (0.2)	13 (<0.1))
Lymphadenopathy	7 (0.1)	3 (<0.1)
Hepatobiliary disorders	7 (0.1)	7 (<0.1)

Source: Table 34 Page 63, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; TEAE=treatment-emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
Note: Follow-up time is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cut-off (August 18, 2022).

Imbalances were noted with higher percentages of participants experiencing unsolicited adverse events in the Placebo to Original Monovalent group under multiple System Organ Classes including general disorders and administration site conditions, nervous system disorders, respiratory, thoracic, and mediastinal disorders, musculoskeletal and connective tissue disorders, and gastrointestinal disorders. As both groups were vaccinated, the clinical significance of these imbalances is unclear.

The frequency and percentage of participants experiencing unsolicited adverse events within 28 days after receiving the second vaccination during the Blinded Crossover Vaccination Period for the Safety Analysis Set are presented in the table below summarizing demographics and baseline characteristics.

Table 26. Frequency and Percentage of Unsolicited Adverse Events Within 28 Days After the Second Vaccination During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Subgroup	Placebo to Original Monovalent n/N (%)	Original Monovalent to Placebo n/N (%)
All participants	3088/6416 (48.1)	3730/15298 (24.4)
Age	--	--
Participants 18 to <65 years	2796/5686 (49.2)	3270/13576 (24.1)
Participants ≥65 years	292/730 (40.0)	460/1722 (11.4)
Sex	--	--
Male	1405/3191 (44.0)	1672/7913 (21.1)
Female	1683/3225 (52.2)	2058/7385 (27.9)

Subgroup	Placebo to Original Monovalent n/N (%)	Original Monovalent to Placebo n/N (%)
Race	--	--
White	2316/4651 (49.8)	2797/11394 (24.5)
Black or African American	312/880 (35.3)	428/1810 (23.6)
Asian	144/255 (56.5)	131/636 (20.6)
American Indian or Alaska Native	224/467 (48.0)	249/1049 (23.7)
Native Hawaiian or Other Pacific Islander	3/8 (37.5)	11/40 (27.5)
Multiple	69/116 (59.5)	87/273 (31.9)
Not Reported	16/34 (47.1)	25/89 (28.1)
Ethnicity	--	--
Not Hispanic or Latino	2386/4898 (48.7)	2887/11801 (24.5)
Hispanic or Latino	694/1501 (46.2)	828/3452 (24.0)
Country[1]	--	--
United States	539/5989 (9.0)	902/14308 (6.3)
Mexico	18/427 (4.2)	38/990 (3.8)
Co-morbidities[a]	--	--
Obesity (BMI ≥30 kg/m^2)	239/2603 (9.2)	393/5763 (6.8)
Chronic lung disease	90/958 (9.4)	186/2187 (8.5)
Chronic kidney disease	5/53 (9.4)	17/112 (15.2)
Cardiovascular disease	14/80 (17.5)	17/172 (9.9)
Diabetes mellitus type 2	57/590 (9.7)	104/1203 (8.6)
High risk status[a]	--	--
High risk	533/6128 (8.7)	898/14586 (6.2)
Not high risk	24/288 (8.3)	42/712 (5.9)

Source: Table 45 Page 85, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: BMI=body mass index; MedDRA=Medical Dictionary for Regulatory Activities; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; TEAE=treatment-emergent adverse event; kg/m^2=kilogram per square meter.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
Note: Follow-up time is defined as time from first crossover dose to the earliest date of early termination, date corresponding to the post-crossover Day 49 assessment, date of death and date of data cut-off (August 18, 2022).
a. Subgroup analyses for country, co-morbidities, and high-risk status were not rerun using updated data.

With the exception of chronic kidney disease (Placebo to Original Monovalent 9.4% versus Original Monovalent to Placebo 15.2%) the percentages of participants who experience an unsolicited adverse event were either comparable or higher in the Placebo to Original Monovalent group compared with Original Monovalent to Placebo group for all of the subgroups analyzed in the table above. The reason for the higher percentages of events in the Placebo to Original Monovalent group was because the datasets were reformatted such that Daily Symptom Diary data were included in the unsolicited adverse event analyses, and most of these events were due to reactogenicity reactions that resulted from subjects receiving the vaccine during the crossover period. The clinical significance of this is unclear, but this analysis does not provide clear evidence to suggest that the safety profile of the vaccine for any of the above subgroups is different from the overall safety population.

For both the Placebo to Original Monovalent and Original Monovalent to Placebo groups, there were higher percentages of participants with SAEs in the 18 to <65 years of age group compared with the ≥65 years of age group (49.2% versus 40.0% and 24.1% versus 11.4%). In addition, the Placebo to Original Monovalent and Original Monovalent to Placebo groups had higher percentages of females with SAEs compared with males (52.2% versus 44.0% and 27.9% and 21.1% respectively). The percentages of participants who experienced SAEs were reasonably balanced in the Original Monovalent to Placebo group between different racial

groups. In the Placebo to Original Monovalent, there were higher percentages of SAEs in the White, Asian, and Multiple subgroups (49.8%, 56.5%, and 59.5%, respectively) compared with the other racial subgroups. The percentage of participants who experienced SAEs in the U.S. was roughly twice as high as those seen in Mexico for both the Placebo to Original Monovalent and Original Monovalent to Placebo groups (9.0% versus 4.2% and 6.3 versus 3.8%, respectively). Save for cardiovascular disease in the Placebo to Original Monovalent group (17.5%) and chronic kidney disease in the Original Monovalent to Placebo group (15.2%), both of which were slightly higher, the rest of the risk factors had comparable percentages of participants who experienced SAEs for both treatment groups. The percentages of participants with a high-risk status were comparable to those with low-risk status for both treatment groups.

Clinical Reviewer Comment: The safety profile during the blinded crossover period was comparable to the initial vaccine period. It is unclear how to interpret the unsolicited adverse event data during the blinded crossover period when the Symptom Diary data were added, but it is unlikely that the safety profile of the vaccine between the initial vaccine and blinded crossover period are substantially different. Based on subgroup analyses, the safety profile of the vaccine in these subgroups is likely comparable to the safety profile of the vaccine in the overall safety population, but the limited interpretability of the data and the lack of a placebo comparator group in this part of the study limits the ability to draw definitive conclusions.

Booster Vaccination Period

A summary of the frequency and percentage of unsolicited adverse events during the Booster Vaccination Period for the safety analysis set are summarized in the table below. For Race, there were slightly higher percentages of participants with SAEs who were White, Asian, or multiple compared with the other subgroups.

Table 27. Frequency and Percentage of Unsolicited Adverse Events During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

Participants Reporting at Least One	Original Monovalent Booster N=13353 n (%)
Unsolicited TEAEs through 28 days after booster dose	--
Unsolicited TEAE	1913 (14.3)
Related unsolicited TEAE	92 (0.7)
Severe unsolicited TEAE	327 (2.4)
Related severe unsolicited TEAE	11 (<0.1)
MAAE	334 (2.5)
Unsolicited TEAEs through data cut-off date	--
Any MAAE	501 (3.8)
Related MAAE	33 (0.2)
SAE	227 (1.7)
Related SAE	6 (<0.1)
AESI (PIMMCs)	18 (0.1)
Related AESI (PIMMCs)	2 (<0.1)
AESIs relevant to COVID-19	9 (<0.1)
Related relevant to COVID-19	0
Deaths	10 (<0.1)
TEAE leading to study discontinuation	11 (<0.1)
Related TEAE leading to study discontinuation	0

Source: Table 30 Page 57, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; n=unique number of participants experiencing the adverse event; N=number of participants in the Booster

Safety Analysis Set; PIMMCs=potential immune-mediated medical conditions; SAE=serious adverse event; TEAE=treatment emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.

The percentages of participants who experienced either an unsolicited TEAE (14.3%) or a related unsolicited TEAE (0.7%) were lower than those seen during the other two treatment periods. The percentages of participants who experienced MAAEs, SAEs, AESIs, Deaths, and TEAEs leading to discontinuation were also comparable to the other treatment periods.

The frequency and percentage of participants in the Safety Analysis Set who experienced unsolicited adverse events, with an occurrence >0.1%, during the Booster Vaccination Period are presented in the table below by system organ class and preferred term.

Table 28. Frequency and Percentage of Unsolicited Adverse With Occurrence in ≥0.1% of Participants During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Any TEAE within 28 days of booster vaccination	1913 (14.3)
Respiratory, thoracic and mediastinal disorders	881 (6.6)
Cough	349 (2.6)
Rhinorrhea	697 (5.2)
Nasal congestion	696 (5.2)
Dyspnea	138 (1.0)
Nervous system disorders	703 (5.3)
Headache	642 (4.8)
Anosmia	57 (0.4)
Ageusia	56 (0.4)
General disorders and administration site conditions	607 (4.5)
Fatigue	296 (2.2)
Pain	281 (2.1)
Chills	186 (1.4)
Pyrexia	175 (1.3)
Gastrointestinal disorders	385 (2.9)
Diarrhea	241 (1.8)
Nausea	188 (1.4)
Vomiting	188 (1.4)
Musculoskeletal and connective tissue disorders	335 (2.5)
Myalgia	278 (2.1)
Infections and infestations	217 (1.6)
Asymptomatic COVID-19	78 (0.6)
Upper respiratory tract infection	26 (0.2)
Viral infection	18 (0.1)
Injury, poisoning and procedural complications	41 (0.3)
Metabolism and nutrition disorders	29 (0.2)
Skin and subcutaneous tissue disorders	29 (0.2)
Psychiatric disorders	28 (0.2)
Vascular disorders	20 (0.1)
Hypertension	14 (0.1)

System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Investigations	16 (0.1)
Cardiac disorders	15 (0.1)

Source: Table 36 Page 68, eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; TEAE=treatment-emergent adverse event.
Note: AEs were classified as TEAEs or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
Note: Follow-up time is defined as time from booster dose to the earliest date of early termination, date corresponding to the post-booster Day 49 assessment, date of death and date of data cut-off (August 18, 2022).

These data do not suggest a safety signal when the prototype vaccine was given to previously vaccinated individuals as a third dose. The percentages of participants who experienced unsolicited TEAEs during the booster period were either comparable or lower than those seen in the other two safety periods.

Severe Unsolicited Adverse Events

For the blinded pre-crossover vaccination period, the percentages of individuals who experienced a severe unsolicited adverse event were balanced between the vaccine and placebo groups (Original Monovalent 5.3% versus Placebo 5.7%). The percentages of individuals experiencing a given unsolicited adverse event were generally low (<0.1%), and there was balance between the vaccine and placebo groups. The exception was fatigue, where the percentages were 4.7% in the vaccine group and 5.1% in the placebo group.

For the blinded crossover vaccination period, the percentages of individuals who experienced a severe unsolicited adverse event were 16.0% in the Placebo to Original Monovalent group versus 4.9% in the Original Monovalent to Placebo group. The most common severe unsolicited adverse event during the blinded crossover vaccination period was fatigue, which was reported by 15.6% participants in the Placebo to Original Monovalent group versus 4.5% of participants in the Original Monovalent to Placebo group. All other severe unsolicited adverse events were reported in less than 0.1% of participants during the blinded crossover period.

For the blinded crossover vaccination period, the percentage of individuals who experienced a severe unsolicited adverse event was 2.4%. Fatigue (2.1%) was the most common severe unsolicited adverse event during the booster period.

Medically Attended Adverse Events

The frequency and percentage of Treatment-Related Medically Attended Adverse Events by System Organ Class and Preferred after the first dose in the series in >1 participant in the Original Monovalent Group during the Initial Vaccination Period for the Safety Analysis Set is presented in the table below.

Table 29. Frequency and Percentage of Treatment-Related Medically Attended Adverse Events by System Organ Class and Preferred Term Reported After First Dose Within the Series in >1 Participant in the Original Monovalent Group During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=847 n (%)
Any System Organ Class	102 (0.5)	25 (0.3)
Skin and subcutaneous tissue disorders	19 (<0.1)	3 (<0.1)
Urticaria	7 (<0.1)	1 (<0.1)
Rash	3 (<0.1)	1 (<0.1)
Angioedema	2 (<0.1)	0
Nervous system disorders	18 (<0.1)	3 (<0.1)
Dizziness	6 (<0.1)	0
Headache	4 (<0.1)	0
Hypoesthesia	2 (<0.1)	0
Migraine	2 (<0.1)	1 (<0.1)
Neuropathy peripheral	2 (<0.1)	0
Musculoskeletal and connective tissue disorders	15 (<0.1)	2 (<0.1)
Arthritis	3 (<0.1)	0
Muscle spasms	3 (<0.1)	0
Pain in extremity	2 (<0.1)	0
Rheumatoid arthritis	2 (<0.1)	0
Infections and infestations	13 (<0.1)	4 (<0.1)
Viral infection	4 (<0.1)	1 (<0.1)
Herpes zoster	2 (<0.1)	0
Gastrointestinal disorders	7 (<0.1)	6 (<0.1)
Abdominal pain upper	2 (<0.1)	1 (<0.1)
Diarrhea	2 (<0.1)	4 (<0.1)
General disorders and administration site conditions	10 (<0.1)	2 (<0.1)
Chest pain	3 (<0.1)	0
Chills	3 (<0.1)	0
Fatigue	2 (<0.1)	0
Vascular disorders	5 (<0.1)	2 (<0.1)
Hypertension	5 (<0.1)	2 (<0.1)
Psychiatric disorders	5 (<0.1)	0
Anxiety	4 (<0.1)	0
Ear and labyrinth disorders	5 (<0.1)	0
Tinnitus	3 (<0.1)	0
Blood and lymphatic system disorders	5 (<0.1)	2 (<0.1)
Lymphadenopathy	3 (<0.1)	2 (<0.1)
Cardiac disorders	5 (<0.1)	0
Eye disorders	5 (<0.1)	0
Uveitis	2 (<0.1)	0
Investigations	3 (<0.1)	0
Blood pressure increased	2 (<0.1)	0
Respiratory, thoracic, and mediastinal disorders	2 (<0.1)	3 (<0.1)
Cough	2 (<0.1)	1 (<0.1)

Primary System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=847 n (%)
Injury, poisoning and procedural complications	2 (<0.1)	0
Reproductive system and breast disorders[a]	1 (<0.1)	1 (<0.1)
Intermenstrual bleeding[a]	1 (<0.1)	0

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Table 36 Page 68
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
a. An extra event of Reproductive System and Breast Disorders/Intermenstrual bleeding was erroneously included in the original CSR.

There were no imbalances in the percentages of participants who experienced treatment related MAAEs in the Original Monovalent 0.5% and Placebo 0.3% groups. There are no individual treatment related MAAEs that occurred in more than 0.1% of participants in the Original Monovalent group during the Initial Vaccination Period.

The Applicant conducted subgroup analyses of MAAEs reported during the Initial Vaccination Period. A table are not presented here; however, the relevant points of the analyses will be analyzed. There were no imbalances in the percentages of MAAEs in the vaccine and placebo groups for any of the subgroups analyzed. There were no imbalances in the percentages of MAAEs between vaccinated individuals 18 to <65 years of age and individuals >65 years of age. There were also no imbalances seen in the percentages of MAAEs in vaccinated males versus females. The percentages of MAAEs were comparable between the different racial and ethnicity groups and between individuals who participated in the Study in the United States versus Mexico. There were slightly higher percentages of vaccinated participants with chronic kidney disease and cardiovascular disease compared with the other medical co-morbidities (12.7% and 11.3% compared with 5.6 - 7.3%). Vaccinated High Risk patients had slightly higher but comparable percentages of MAAEs compared with Not High-Risk patients (5.1% and 3.3% respectively).

The frequency and percentage of treatment-related medically attended adverse events by system organ class and preferred term after the first dose in the series in >1 participant in the Original Monovalent Group during the Blinded Crossover Period for the Safety Analysis Set is presented in the table below.

Table 30. Frequency and Percentage of Treatment-Related Medically Attended Adverse Events by System Organ Class and Preferred Term Reported After First Dose Within the Series in >1 Participant in the Placebo to Original Monovalent Group During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Any System Organ Class	26 (0.4)	29 (0.2)
Skin and subcutaneous tissue disorders	5 (<0.1)	4 (<0.1)
Urticaria	3 (<0.1)	0
Nervous system disorders	2 (<0.1)	11 (<0.1)
Musculoskeletal and connective tissue disorders	5 (<0.1)	4 (<0.1)
Pain in extremity	2 (<0.1)	2 (<0.1)

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Gastrointestinal disorders	4 (<0.1)	7 (<0.1)
Diarrhea	2 (<0.1)	3 (<0.1)
Vomiting	2 (<0.1)	0
General disorders and administration site conditions	3 (<0.1)	7 (<0.1)
Respiratory, thoracic, and mediastinal disorders	2 (<0.1)	4 (<0.1)
Metabolism and nutrition disorders	2 (<0.1)	0
Vascular disorders	2 (<0.1)	0

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 122, Page 252
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.

There were no individual treatment related MAAEs that occurred in more than 0.1% of participants during the Blinded Crossover Period. In general, the safety profiles for both crossover groups were similar to what was observed during the Initial Vaccination Period.

Subgroup analyses for the percentages of participants who experienced MAAEs during the Blinded crossover period were also similar to what was observed during the Initial Vaccination Period.

Table 31. Frequency and Percentage of Treatment-Related Medically Attended Adverse Events by System Organ Class and Preferred Term Reported in ≥3 Participants During the Booster Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Infections and infestations	4 (<0.1)
Cellulitis	2 (<0.1)
Conjunctivitis	1 (<0.1)
Rhinitis	1 (<0.1)
Investigations	3 (<0.1)
Heart rate increased	1 (<0.1)
Hepatic enzyme increased	1 (<0.1)
SARS-CoV-2 test positive	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	3 (<0.1)
Acute respiratory failure	1 (<0.1)
Asthma	1 (<0.1)
Pleuritic pain	1 (<0.1)
Pulmonary embolism	1 (<0.1)
Cardiac disorders	2 (<0.1)
Acute myocardial infarction	1 (<0.1)
Atrial fibrillation	1 (<0.1)
Blood and lymphatic system disorders	1 (<0.1)
Lymphadenopathy	1 (<0.1)
Hepatobilliary disorders	1 (<0.1)
Cholecystitis	1 (<0.1)
Injury, poisoning and procedural complications	1 (<0.1)
Postvaccination syndrome[a]	1 (<0.1)
Metabolism and nutrition disorders	1 (<0.1)
Hypokalemia	1 (<0.1)

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (<0.1)
Nasopharyngeal neoplasm benign	1 (<0.1)
Nervous system disorders	2 (<0.1)
Dizziness	1 (<0.1)
Headache	1 (<0.1)
Reproductive system and breast disorders	1 (<0.1)
Dysmenorrhea	1 (<0.1)
Vascular disorders	1 (<0.1)
Deep vein thrombosis	1 (<0.1)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 123, Page 254-255
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Booster Safety Analysis Set; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2
Note: AEs were classified as treatment-emergent adverse events (TEAEs) or post-treatment and defined as any AE that was newly developed at or after the first dosing date of trial vaccine.
a. Post-vaccination syndrome (PVS) or post-acute COVID-19 vaccination syndrome (PACVS) is characterized by symptoms such as exercise intolerance, excessive fatigue, numbness, brain fog, neuropathy, insomnia, palpitations, myalgia, tinnitus or humming in ears, headache, burning sensations, and dizziness.

There were no individual treatment related MAAEs that occurred in more than 0.1% of participants during the Booster Vaccination Period. In general, the safety profile of the booster dose for both crossover groups were similar to what was observed during the Initial Vaccination Period.

> *Clinical Reviewer Comment: In summary, there were low percentages of participants who experienced treatment-related unsolicited adverse events or treatment-related medically attended adverse events overall. No imbalances were noted in the placebo-controlled pre-crossover period, with generally similar types of events and time of onset. Percentages of events were also low in the blinded crossover and booster vaccination periods. There was no clear evidence for a safety signal based on the unsolicited adverse event data for Adult Main Study 301.*

6.1.12.3 Deaths

Introduction

The percentages of participants who experienced an adverse event leading to death were low overall. No imbalances were noted in the placebo-controlled initial vaccine period.

There were 8 SAEs that used “death” as the preferred term in the post-crossover and booster vaccination periods. In seven of these cases, the death was not explained or attributed to natural causes. In the other case, the participant likely died due to complications from metastatic cancer. On February 25, 2025, an information request was sent to the Applicant asking for more information on the unexplained deaths and two of the more concerning cardiac deaths. The Applicant responded that no further information was available for these cases.

During the post-crossover and booster vaccination periods, there were multiple cardiac-related fatalities with a temporal relationship within 30 days of vaccine administration. These types of cases were also noted during the initial vaccination period; however, there is no comparator group in the post-crossover period to assess for the relative risk difference between participants receiving the vaccine versus placebo. When the cases of cardiac arrest are considered together with the 7 unexplained deaths, the clinical concern for cardiac pathology that could be related to

vaccination increases. However, given the lack of a temporal relationship between vaccine administration and the unexplained death events, vaccine relatedness is highly unlikely.

Based on a numerical imbalance in nonfatal atrial fibrillation cases (discussed in Section 6.1.12.4 Nonfatal Serious Adverse Events), atrial fibrillation was added to the Applicant's postmarketing surveillance which also includes myocarditis/ pericarditis, arrhythmia, and hemorrhagic and non-hemorrhagic stroke. Though there is uncertainty about whether the clinical trial data has captured all potential safety signals that might have contributed to these fatal events, the postmarketing surveillance captures key potential causes of both temporally associated cardiac arrest and non-temporally associated death (i.e. atrial fibrillation, arrhythmia, and hemorrhagic and no-hemorrhagic stroke). Cardiac failure, cardiomyopathy, atrial fibrillation, and myocarditis/ pericarditis will be addressed in the U.S. Prescribing Information.

Pre-Crossover Period

Death occurred in 11 (<0.1%) participants in the Original Monovalent arm and 8 (<0.1%) participants in the placebo arm in the pre-crossover period to the data cutoff date of August 18, 2022. None of the deaths in the Original Monovalent arm were assessed by the Applicant as being related to the vaccine. The frequency and percentage of adverse events leading to death are presented in the table below.

Table 32. Frequency and Percentage of Adverse Events Resulting in Death by System Organ Class and Preferred Term During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	**Original Monovalent N=19735 n (%)**	**Placebo N=9847 n (%)**
Participants experiencing an event resulting in death	11 (<0.1)	7 (<0.1)
Cardiac disorders	6 (<0.1)	5 (<0.1)
Cardiac arrest	5 (<0.1)	4 (<0.1)
Myocardial infarction	1 (<0.1)	1 (<0.1)
Injury, poisoning, and procedural complications	3 (<0.1)	0
Accidental overdose	1 (<0.1)	0
Gun shot wound	1 (<0.1)	0
Toxicity to various agents	1 (<0.1)	0
Infections and infestations	1 (<0.1)	1 (<0.1)
Septic shock	1 (<0.1)	0
COVID-19 pneumonia	0	1 (<0.1)
Nervous system disorders	1 (<0.1)	0
Cerebrovascular accident	1 (<0.1)	0
General disorders and administration site conditions	0	1 (<0.1)
Death	0	1 (<0.1)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month CSR, Table 66 Page 111
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm

Deaths in the pre-crossover Original Monovalent arm were associated with cardiac arrest (n=5), myocardial infarction (n=1), toxicity to various agents (n=1), accidental overdose (n=1), cerebrovascular accident (CVA) (n=1), gunshot wound (n=1), and septic shock (n=1). Deaths in the placebo arm were associated with cardiac arrest (n=4), myocardial infarction (n=1), COVID-19 (n=1), and COVID-19 pneumonia (n=1).

Of the 11 deaths in the Original Monovalent arm, 4 had a clear alternative etiology, including toxicity to various agents (cocaine, fentanyl, and heroin intoxication), accidental overdose (alcohol and prescription drugs), gunshot wound to the head, and septic shock (pneumonia and blood cultures positive for *Streptococcus pneumoniae*). The narrative information for 6 of the remaining 7 deaths is summarized below. One of the cases of cardiac arrest was not included in the narratives for unclear reasons. Unless otherwise stated, the time intervals between vaccination and a given event exclude days of administration.

- A 75-year-old female participant with a history of hypertension and coronary artery disease experienced a fatal CVA (b) (6) days following the second dose of Original Monovalent. The participant presented to the hospital with left side weakness, confusion, left sided facial droop, and altered mental status. A chest X-ray showed bibasilar pneumonia with pulmonary edema. A computed tomography angiogram (CTA) of neck showed acute occlusion in the proximal to mid portion of the right internal carotid artery with extension into the intracranial region and right middle cerebral artery (MCA). A CTA of the head demonstrated acute occlusion of the right intracranial internal carotid artery and right MCA without collaterals. A CT brain perfusion showed a large core infarct in the territory of the right middle cerebral artery with a small area of penumbra. A thrombectomy and thromboaspiration via angiography was performed. Following the thrombectomy, the participant was noted to be paralyzed on her right side. Following thrombectomy, repeat imaging revealed hemorrhagic conversion of ischemic CVA. Despite a right decompressive craniotomy, the events were fatal.

Clinical Reviewer Comment: CVA is a key clinical concern of this review given the numerical imbalances that occur in participants who experienced CVA and atrial fibrillation during the pre-crossover period. In this case, there was no evidence for atrial fibrillation. Furthermore, the participant was elderly, had CVA risk factors, and the event did not have a clear temporal relationship to the vaccine given that it fell outside of a 30- and 42-day risk window. In summary, there is no clear temporal relationship and a likely alternative explanation for this event, which makes vaccine relatedness to this CVA event less likely.

- A 79-year-old white female participant whose relevant medical history included hypertension, hyperlipidemia, sleep apnea, cardiac pacemaker in situ-Medtronic single chamber placement, and obesity (BMI=43.4 kg/m^2) experienced a fatal myocardial infarction (b) (6) days following the second dose of Original Monovalent. She was hospitalized for chest pain and transferred to the intensive care unit. At the time of transfer, she was found to be in cardiogenic shock and received aggressive resuscitation, with placement of a central line. A stat echocardiogram showed a left ventricular ejection fraction of less than 25%. The participant had a principal problem of ventricular fibrillation and an active problem of acute systolic congestive heart failure. A cardiac catheterization revealed a complete occlusion of the left main coronary artery and 90% occlusion of the right coronary artery. As no target was identified for grafting, the participant was judged not to be a candidate for coronary artery bypass grafting and the myocardial infarction was assessed as a non-survivable event. The participant was transitioned to comfort care, and she subsequently expired the same day. An autopsy was not performed, and the death certificate was not available. The event was considered fatal. This participant's age and co-morbidities are significant risk factors for myocardial infarction.

Clinical Reviewer Comment: In the context of these risk factors and temporal distance from vaccination (>2 months), the Applicant's and investigator's assessment that the event is not related to the study vaccine is considered reasonable.

- A 66-year-old white male participant with no significant past medical history experienced cardiac arrest (b) (6) days after receiving the first initial vaccination of Original Monovalent. The participant was found outside of a store, unresponsive, pulseless, face down, and apneic. He was taken to the emergency department where he received advanced life support. A limited transthoracic echocardiogram revealed ventricular fibrillation; no pericardial effusion was noted. No other laboratories/diagnostic tests were performed. The participant was ultimately pronounced dead. The cause of death was reported as cardiac arrest. An autopsy was not performed. The death certificate was not available.

Clinical Reviewer Comment: Given the temporal association and lack of risk factors, vaccine relatedness cannot be excluded.

- A 40-year-old black or African American male participant with a history of asthma, Type 1 diabetes mellitus, hypertension, neuropathy, post-traumatic stress disorder, insomnia, bipolar disorder, current nicotine dependency, and current illicit drug use developed cardiac arrest 23 days after receiving the second initial vaccination of Original Monovalent. The participant presented to the emergency department (ED) unresponsive status-post cardiac arrest via emergency medical service (EMS). No shocks were administered in the field. Cardiovascular examination revealed him to be hypotensive, pulseless, and apneic. The Glasgow coma scale score was 3. He was treated with Levophed and intravenous (IV) fluids as he was hypotensive and unstable. An endotracheal tube was placed for protection of the airway for respiratory support and failure. As the participant remained in pulseless electrical activity (PEA), he was treated with 2 doses of IV epinephrine and 1 dose of calcium gluconate for concern of hypokalemia, as per advanced cardiovascular life support protocol. He had return of spontaneous circulation after several rounds of advanced cardiovascular life support. A urine drug screen was positive for cocaine and tetrahydrocannabinol. An aspartate aminotransferase of 993 (units and reference range not provided) was reported. Assessment was status post-PEA arrest after suspected drug overdose, polysubstance abuse, new onset cardiomyopathy, acute renal failure, acute hypoxemic respiratory failure, and severe anoxic encephalopathy. He was admitted to the ICU. A magnetic resonance imaging scan revealed evidence of significant anoxic injury. The participant intermittently required vasopressors. A neurological examination revealed no brainstem reflexes. Over the next 24-48 hours, the participant was monitored for neurological function; however, the initial presentation suggested a poor prognosis. He was transitioned to comfort care. The participant ultimately died. An autopsy was not performed, and a death certificate was not obtained.

Clinical Reviewer Comment: There was a clear temporal association between vaccine administration and the cardiac arrest; however, the participant had multiple cardiac risk factors. Furthermore, there is reasonable clinical evidence that this participant was actively using cocaine (positive urine drug screen), and there is a diagnosis of "suspected drug overdose" which likely explains the cardiac arrest. The temporal relationship between vaccine administration and the event cannot be discounted, and vaccine relatedness cannot be entirely excluded; however, given the facts in this narrative, vaccine relatedness is unlikely.

- A 50-year-old American Indian or Alaska Native male participant with a history of insulin-dependent type 2 diabetes mellitus, hypertension, bilateral diabetic foot ulcers, chronic alcohol use, and bilateral peripheral diabetic neuropathy of the feet experienced cardiac arrest (b) (6) days after receiving the second initial vaccination of Original Monovalent. The participant experienced acute pulseless cardiovascular collapse. He arrived at the

emergency room as a suspected death on arrival after being pulseless for approximately 30-45 minutes. He received cardiopulmonary resuscitation (CPR), advanced cardiac life support, and was intubated and ventilated. The participant had very coarse breath sounds bilaterally with poor ventilation on the left due to a mucous plug and was hard to ventilate. He expired. He was noted to have a bilateral foot infection upon physical examination. Laboratory results included white blood cells of 8.3 K/cm (reference range: 4.8-10.8), hematocrit of 26.4% (reference range: 40.0-52.0), and platelet count of 112 (unit and reference ranges not reported). The death certificate noted the immediate cause of death as possible cardiac failure, history of hypertension as an underlying cause, and other significant conditions contributing to death as alcohol abuse and diabetes mellitus. The manner of death was noted as natural causes. An autopsy was not performed.

Clinical Reviewer Comment: There was a temporal association between the cardiac arrest and vaccine administration using a 42-day window. While the patient did have risk factors for cardiovascular disease, the narrative isn't definitive about the cause of the cardiac arrest. With the death certificate stating "possible cardiac failure and a history of hypertension" in mind, this participant was only on a single blood pressure medication (lisinopril), and he had no documented history of congestive heart failure. While acknowledging the congestive heart failure risk factors, including poorly controlled diabetes (evidenced by the foot ulcers), as a plausible mechanism for the cardiac arrest, the temporal relationship between the event and vaccination along with a lack of clear explanation for the cardiac arrest makes vaccine relatedness, though unlikely, unable to be entirely excluded.

- A 45-year-old female participant from the U.S. with a past medical history of amphetamine abuse, asthma, nicotine dependence, hypertension, hysterectomy due to a fibroid, and obesity with a BMI of 40.7 kg/m^2 developed cardiac arrest approximately (b) (6) days after receiving the first initial Original Monovalent vaccination. On the date of death, an ambulance was called, and paramedics responded to the scene and found the participant unresponsive upon arrival with no carotid pulse. Cardiopulmonary resuscitation was attempted but unsuccessful. She was pronounced dead due to cardiac arrest and not transported to the hospital. The participant had recently been treated for cellulitis of the right forearm and otitis externa. She was noted to be slightly hypertensive during the observation period after vaccine administration, with mild wheezing that was not considered clinically significant. It was unknown if an autopsy was performed, and a death certificate was not available.

Clinical Reviewer Comment: The patient did have risk factors for cardiovascular disease, but the cause of the cardiac arrest was not determined. Given her younger age and the temporal association between the cardiac arrest and vaccine administration, vaccine relatedness, though unlikely, cannot be entirely excluded with the information provided.

Summary Reviewer Comment: There is no imbalance in the percentage of participants who experienced cardiac arrest events for the vaccine and placebo groups in the pre-crossover period. However, several of the cardiac arrest events in the vaccine and placebo groups were temporally related to vaccine administration. After careful consideration of the narrative information, there is insufficient evidence to conclude that cardiac arrest was a safety signal during the initial vaccination period. However, the suspicious nature of some of these cases (i.e. the close temporal relationship to vaccination) was a consideration in concluding that atrial fibrillation was a potential safety signal (discussed in Section 6.1.12.4)

Post-Crossover Period

The frequency and percentage of adverse events leading to death during the blinded crossover period are summarized in the table below.

Table 33. Frequency and Percentage of Adverse Events Resulting in Death by System Organ Class and Preferred Term During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Participants experiencing an event resulting in death	10 (0.2)	30 (0.2)
Injury, poisoning and procedural complications	4 (<0.1)	4 (<0.1)
Road traffic accident	2 (<0.1)	2 (<0.1)
Toxicity to various agents	1 (<0.1)	2 (<0.1)
Accidental overdose	1 (<0.1)	0
Vascular disorders	2 (<0.1)	0
Aneurysm ruptured	1 (<0.1)	0
Arteriosclerosis	1 (<0.1)	0
Cardiac disorders	1 (<0.1)	7 (<0.1)
Cardiac arrest	1 (<0.1)	2 (<0.1)[a]
Acute myocardial infarction	0	1 (<0.1)[b]
Cardiac failure congestive	0	1 (<0.1)
Cardiomyopathy	0	1 (<0.1)
Cardiomyopathy alcoholic	0	1 (<0.1)
Myocardial infarction	0	1 (<0.1)
General disorders and administration site conditions	1 (<0.1)	9 (<0.1)
Death	0	7 (<0.1)
Multiple organ dysfunction syndrome	1 (<0.1)	2 (<0.1)
Infections and infestations	1 (<0.1)	4 (<0.1)
Septic shock	1 (<0.1)	1 (<0.1)
COVID-19 pneumonia	0	1 (<0.1)
Emphysematous pyelonephritis	0	1 (<0.1)
Pneumonia aspiration	0	1 (<0.1)[c]
Respiratory, thoracic, and mediastinal disorders	0	5 (<0.1)
Chronic obstructive pulmonary disease	0	5 (<0.1)[a,d]
Respiratory failure	0	1 (<0.1)[d]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (<0.1)	0
Angiosarcoma	1 (<0.1)	0
Metabolism and nutrition disorders	0	1 (<0.1)
Diabetes mellitus	0	1 (<0.1)[b]
Nervous system disorders	0	1 (<0.1)
Ischemic stroke	0	1 (<0.1)[c]
Psychiatric disorders	0	1 (<0.1)
Completed suicide	0	1 (<0.1)
Social circumstances	0	1 (<0.1)
Victim of homicide	0	1 (<0.1)

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report Table 179, page 399-400
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; PT=preferred term
a. 1 participant was included under both PTs of cardiac arrest and chronic obstructive pulmonary disease.
b. 1 participant was included under both PTs of acute myocardial infarction and diabetes mellitus.
c. 1 participant was included under both PTs of ischemic stroke and pneumonia aspiration.
d. 1 participant was included under both PTs of chronic obstructive pulmonary disease and respiratory failure.

In the post-crossover period, there were a total of 40 deaths, 10 (0.2%) in the Placebo to Original Monovalent group and 30 (0.2%) Original Monovalent to Placebo group); 22 of these deaths either had no temporal relationship to vaccine administration and/ or had clear alternative etiologies including road traffic accident, toxicity to various agents, accidental overdose, multiple organ dysfunction syndrome, septic shock, COVID-19 pneumonia, emphysematous pyelonephritis, chronic obstructive pulmonary disease, angiosarcoma, completed suicide, and victim of homicide. The remaining events are as follows:

- There were 2 participants in the Placebo to Original Monovalent Group whose deaths were attributed to vascular disorders, 1 participant with arteriosclerosis, and 1 participant with aneurysm rupture. The narratives for these 2 cases are summarized as follows:
    - An 82-year-old Black or African American male participant with a history of dyslipidemia, type 2 diabetes mellitus, hypertension, obesity, gastroesophageal reflux disease, and prostate cancer died (b) (6) days after receiving Original Monovalent as the second crossover vaccination. This participant was found dead at home, and atherosclerotic cardiovascular disease was the reported cause of death. No diagnostic or laboratory tests were performed, and no treatment medications were given. No autopsy was performed, and a death certificate was not available. Though it could be reasonably presumed that this participant had cardiovascular disease, the narrative specifically states that the participant "had no previous history of atherosclerotic cardiovascular disease." There is no cardiac catheterization data presented in the narrative.

Clinical Reviewer Comment: Though there is no clear temporal relationship between this death and vaccine administration and because this participant had multiple risk factors for cardiovascular disease it is unlikely that this death was due to vaccine administration. No other information has been provided that would suggest vaccine relatedness.

    - A 35-year-old American Indian or Alaska Native female participant with hypertension, obesity, alcohol use, and tobacco use experienced a traumatic rupture of a left vertebral artery aneurysm with subarachnoid hemorrhage, brain stem herniation, and subsequent brain death one day after the second dose of Original Monovalent vaccine. While incarcerated at the local law enforcement center, she suffered a fall during a sudden witnessed seizure and was found unresponsive in the jail cell. She was treated emergently at the health center and then airlifted to the hospital. In the Emergency Department, she was found to have a GCS eye of 1, GCS verbal of 1, and GCS motor of 3. A head computerized tomography (CT) scan showed a large subarachnoid hemorrhage amidst a widened left vertebral artery and brainstem herniation that resulted in brain death. Treatment medications included intravenous fluids, tranexamic acid, digoxin, calcium chloride, diltiazem, amiodarone, lorazepam, ketamine, levetiracetam, and fentanyl. The participant was intubated but died later that day. An autopsy was performed (reports not available), and a formal death certificate was provided. The immediate cause of death was cerebral anoxia resulting from a rupture of a left vertebral artery aneurysm. Given that this event occurred (b) (6) days after vaccine administration, a temporal association must be considered. While this participant did have risk factors for aneurysm rupture (hypertension, alcohol use, smoking), as written, the narrative indicates that the participant's fall was the result of witnessed seizure activity, which she had no prior history of. This raises the possibility that this participant had a spontaneous left vertebral aneurysm

rupture which resulted in seizure activity and a subsequent fall rather than trauma being the cause of the aneurysm rupture.

Clinical Reviewer Comment: Because of the strong temporal relationship between the aneurysm rupture and vaccine administration, the young age of the patient, and the possibility of spontaneous aneurysm rupture as opposed traumatic aneurysm rupture, the possibility that vaccine reactogenicity may have contributed to this event cannot be entirely excluded.

- 1 participant in the Placebo to Original Monovalent group and 2 participants in the Original Monovalent to Placebo group had cardiac arrest.
    - A 58-year-old White not Hispanic or Latino male participant with a history of hypertension and obesity suffered cardiac arrest (b) (6) days after receiving the second initial vaccination (Original Monovalent). The participant collapsed at home and was transported to the emergency department by ambulance. At the hospital, he was found to be unresponsive. He tested positive for COVID-19 by reverse transcription polymerase chain reaction test. The participant received cardiopulmonary resuscitation for 1 hour and was treated with intraosseous (IO) epinephrine and IO amiodarone once. Cardiac function was not regained, and time of death was declared. An autopsy was not performed, and a death certificate was not available. The cause of death was cardiac arrest. There was no temporal relationship in this case to support attributing the cardiac arrest to vaccine administration.

Clinical Reviewer Comment: Given the lack of a temporal relationship between this event and vaccine administration and the fact that there was an alternative explanation for this death (COVID-19), this death was highly unlikely to be related to study vaccine administration.

- A 69-year-old White Hispanic or Latino male participant with a history of hypertension died of chronic obstructive pulmonary disease (COPD) and cardiac arrest (b) (6) days after receiving the second initial Original Monovalent vaccination. The spouse could not provide further details other than the cause of death as medical condition (COPD) complications. Autopsy was not performed, and a death certificate was not obtained. The participant was not hospitalized in the days preceding his death. No laboratory and diagnostic tests were performed.

Clinical Reviewer Comment: The narrative has inconsistencies. For example, it does not list COPD as part of this participant's past medical history, and he was not receiving any treatments for COPD at the time of his death. His only medications were carvedilol and amlodipine. However, there is no temporal association between this participant's death and vaccine administration, and vaccine relatedness in this case is highly unlikely.

- A 47-year-old White male participant with a BMI of 31.8 kg/m^2 and no other known cardiovascular risk factors developed cardiac arrest 7 days after receiving Original Monovalent as the second crossover vaccination. Concomitant medications included Adderall and Seroquel. The Applicant was otherwise not able to obtain further medical history or details regarding this participant's medical management. No autopsy was performed, and no death certificate could be obtained. The principal investigator assessed this event as not related but did not provide an alternative etiology.

Clinical Reviewer Comment: Seroquel is known to prolong the QT interval, and Adderall is associated with relevant serious adverse events including sudden death in patients with

severe cardiovascular disease, myocardial infarction, hypertension, and cardiomyopathy with long term use. Hypertension can result when these two medications are used together; however, this interaction is more relevant to patients under the age of 18. It is extremely unlikely that any of these adverse events would have occurred in a patient who was regularly being prescribed and otherwise tolerating these medications.

Though there is a potential alternative explanation for this event, there is a strong temporal relationship to the event (7 days after vaccination excluding days of administration). In addition, the participant did not have any cardiovascular risk factors save for a slightly elevated calculated BMI of 31.8 kg/m^2.

This case demonstrates that there is a continuing pattern of temporally associated fatal cardiac events occurring throughout the study. Given that there is no comparator group in the post-crossover period, it is difficult to put this case into a larger context of a risk difference between a vaccine and placebo group. However, when all factors are considered, vaccine relatedness cannot be excluded in this case.

- 5 participants in the Original Monovalent to Placebo group had other fatal cardiac events (acute myocardial infarction, cardiac failure congestive, cardiomyopathy, cardiomyopathy alcoholic, and myocardial infarction), and 1 participant who experienced a myocardial infarction prior to death, but with the final cause of death was unknown. Their narratives are as follows:
    - A 58-year-old African American male participant with a history of acute renal failure with initiation of dialysis, alcohol consumption (2 drinks per day), and smoking (approximately 1 pack of cigarettes per week) died of "cardiomyopathy alcoholic" (b) (6) days after receiving a second Original Monovalent vaccination. The participant presented to an emergency room with jaundice, shortness of breath, and weakness. He was seen in the emergency room for similar complaints 3 days prior and was sent home. The initial medical evaluation demonstrated clinical evidence of multisystem organ failure due to septic shock with cardiogenic shock (international normalized ratio [INR] 14 (reference range: ≤1.1, white blood cell count 15.83 (reference range: 4.5-11.0), total bilirubin 20.7 (reference range: 1.2), and troponin 0.130 (reference range: 0-0.04), units were not provided for laboratory values). An echocardiogram demonstrated an ejection fraction of 19 percent (reference range: 55-70). A computerized tomography scan of the abdomen revealed cardiomegaly, bilateral pleural effusions, and an enlarged liver. A lactate level was also ordered and found to be elevated at 96 (reference range: <2.3). Renal failure was documented, and the participant underwent dialysis. The participant was diagnosed with end stage liver disease based on his model for end-stage liver disease (MELD) score (suggested 100% mortality at 3 weeks). The participant was placed on hospice care in the ICU 14 days after presenting to the emergency department. He died 24 hours later, and the cause of death was listed as cardiomyopathy alcoholic. There was no autopsy performed and no death certificate obtained. The principal investigator assessed this event as severe and not related to the vaccine.

Clinical Reviewer Comment: The narrative does not fully characterize the sepsis (i.e., no documentation of blood cultures being drawn, or antibiotics being administered). Although alcoholic liver disease and alcoholic cardiomyopathy certainly contributed to this patient's death, it is likely that sepsis and multisystem organ failure were the underlying cause of death based on the facts presented in this narrative. However, given the lack of a temporal

association between these medical events and vaccine administration, and because there is a plausible explanation for this participant's death, vaccine relatedness is unlikely.

- A 96-year-old American Indian or Alaska Native Hispanic or Latino male participant with a history of hypertension, diabetes mellitus type 2, and hypercholesterolemia died of an acute myocardial infarction and diabetes mellitus (b) (6) days after receiving the second initial Original Monovalent vaccination. The participant was diagnosed with hypothyroidism and significantly decreased renal function. Laboratory studies were significant for urea of 275 mg/dL (reference range: 16-48.5), blood urea nitrogen (BUN) of 128.5 mg/dL (reference range: 8-23), creatinine of 8.37 mg/dL (reference range: 0.7-1.2), and potassium of 7.5 mEq/L (reference range: 3.5-5.1). He was placed on levofloxacin for a tooth abscess several days before his death. The participant ultimately suffered sudden cardiac death while taking a nap. An autopsy was not performed, and the participant was cremated. There was a reasonable medical explanation for this participant's death and no temporal relationship between his death and vaccine administration was present.

Clinical Reviewer Comment: It is unclear why this participant's renal function was so compromised at the time of his death. His screening labs were not available at the time of this review. Ultimately, vaccine involvement in this fatal cardiac event is unlikely.

- A 62-year-old White Hispanic or Latino male participant with a medical history of hernia repair, right toe surgery, tobacco use, hepatitis C, visual impairment, osteoarthritis, and gastroesophageal disease died from a myocardial infarction (b) (6) days after receiving the second initial Original Monovalent vaccination. No autopsy was performed; no medical records were available as the participant did not sign a medical release form.

Clinical Reviewer Comment: Though there was no temporal relationship between the myocardial infarction and vaccine administration, the lack of information in this narrative makes it difficult to draw definitive conclusions regarding vaccine relatedness to this myocardial infarction. However, vaccine relatedness to this cardiac event is unlikely.

- An 80-year-old White male participant with a history of seasonal allergies, anemia (iron), eczema, tonsillitis, tonsillectomy, depression, cataracts, rheumatoid arthritis, cataract surgery, congestive heart failure, coronary artery bypass surgery (2 vessels), pacemaker placement, gastroesophageal reflux disease (GERD), benign prostatic hyperplasia, melanoma, numbness in left hand, asthma, insomnia, benign cyst in the right kidney, broken right hip, joint surgery, pacemaker replaced, and basal cell carcinoma presented to the hospital (b) (6) days after receiving the second initial Original Monovalent vaccination and subsequently died of congestive heart failure the next day. Further details were not provided. An autopsy was not performed. Death certificate was not obtained. The release of the medical records was declined by the hospital. Given the participant's age, medical comorbidities including congestive heart failure and coronary heart disease, and lack of a temporal relationship to vaccine administration, it is unlikely that this participant's death was related to vaccine administration.

Clinical Reviewer Comment: Given his age, risk factors, and a lack of a temporal relationship between his death and vaccine administration, it is unlikely that this participant's death was related to the study vaccine.

- A 73-year-old White male participant with a history of asthma, hypertension, coronary artery disease, cardiomyopathy, and congestive heart failure died of cardiomyopathy and coronary artery disease (b) (6) days after the second initial dose of Original Monovalent. Several weeks prior to his death, the participant was hospitalized for an acute myocardial infarction. Coronary angiography (cardiac catheterization) showed diffuse diabetic appearing severe coronary arterial disease (CAD). Cardiothoracic surgery was consulted, and coronary artery bypass graft (CABG) surgery was recommended. The participant was discharged to home and re-admitted several days later for the CABG procedure. He underwent CABG x5 with placement of an intra-aortic balloon pump. It was not a planned surgery but was necessary as the participant had severe CAD. He also had a mitral valve replacement and patent foramen ovale closure. He was then admitted to the ICU. After the surgery, he went into respiratory failure, which required intubation, and he was put on a ventilator. He developed shock and peripheral vascular ischemia which required treatment with unspecified vasopressors. The participant had a long hospital course and was ultimately placed on palliative care and was transitioned to hospice care. He developed cardiomyopathy (b) (6) days after the second initial dose of Original Monovalent and died on the same day.

Clinical Reviewer Comment: Given his age, risk factors, and a lack of a temporal relationship between his death and vaccine administration, it is unlikely that this participant's death was related to the study vaccine.

- There were 7 events listed as "Death". This preferred term was used because the cause of death was not obtained by the investigator, or the death was felt to be due to "natural causes." These narratives do not provide sufficient information to exclude vaccine involvement.

Clinical Reviewer Comment: This reviewer acknowledges that there is no clear temporal relationship between these deaths and vaccine administration, making vaccine relatedness less likely. However, because vaccine involvement cannot be entirely excluded in these cases given the lack of information in the narratives, further inquiries were made to the Applicant for additional medical history. The Applicant was unable to provide further information.

- The narratives for the 7 events listed as "Death" are presented below:
  - A 44-year-old White male participant with history of food allergies and a BMI of 43.7 kg/m^2 was found unconscious in the shower with blood coming from his eyes, nose, and mouth (b) (6) days after receiving a second dose of the Original Monovalent vaccine. He never regained consciousness despite receiving cardiopulmonary resuscitation. An autopsy was performed, but the results were not provided. The death certificate was not available.

Clinical Reviewer Comment: The lack of a temporal relationship between this event and vaccine administration makes it unlikely that the Original Monovalent Vaccine contributed to this participant's death.

  - AA 66-year-old White female participant with a history of insomnia and a BMI of 20 kg/m^2 was found deceased at home (b) (6) days after receiving a second dose of Original Monovalent vaccine. She did not receive any medical treatment prior to her death. No death certificate was provided, and it was unknown if an autopsy was performed.

Clinical Reviewer Comment: The lack of a temporal relationship between this event and vaccine administration makes it unlikely that Original Monovalent vaccine contributed to this participant's death.

- An 85-year-old White male participant with a history of metastatic cancer died (b) (6) days after receiving the second dose of Original Monovalent. The cause of death was unknown, but this participant had a complicated medical course, which included deep vein thrombosis, acute myocardial infarction, pneumonia, and urinary tract infection.

Clinical Reviewer Comment: The lack of a temporal relationship between this event and vaccine administration, multiple medical comorbidities, and complicated clinical course make it unlikely that the study vaccine contributed to this participant's death.

- A 42-year-old White male participant with a history of hypertension, obesity (BMI 63.8 kg/m^2), type 2 diabetes mellitus, and hypercholesteremia died at home (b) (6) days after receiving a second dose of Original Monovalent. The death certificate reported the death as natural causes. The participant did not seek medical attention prior to his death, so no further diagnostic information is available.

Clinical Reviewer Comment: The lack of a temporal relationship between this event and vaccine administration makes it unlikely that the study vaccine contributed to this participant's death.

- A 64-year-old White female participant with a history of hypertension, Reiter's syndrome, arrhythmia and mitral valve regurgitation, breast cancer, history of radiation therapy, sleep apnea, and flash pulmonary edema died (b) (6) days after receiving the second dose of Original Monovalent. She suddenly started to experience shortness of breath. Her son attempted to drive her to the hospital; she collapsed in route and required cardiopulmonary resuscitation, which was initiated by the son. She vomited at one point during the rapid chain of events. Paramedics arrived but were unable to revive the participant. The cause of death was reported as natural causes and other contributing conditions included hypertension and mitral valve regurgitation. An autopsy was not performed. Per the medical records, the participant was not hospitalized within the last 6 months.

Clinical Reviewer Comment: The lack of a temporal relationship between this event and vaccine administration along with the multiple cardiac comorbidities make it unlikely that the study vaccine contributed to this participant's death.

- A 64-year-old Arabic male participant with no significant past medical history died (b) (6) days after receiving the second of dose Original Monovalent. His family reported his death to the study site staff after he missed a follow-up appointment. No further details are available regarding his death.

Clinical Reviewer Comment: The lack of a temporal relationship makes it unlikely that study vaccine contributed to this participant's death.

- A 29-year-old American Indian or Alaska Native Hispanic or Latino male participant with a history of depression and allergic rhinitis died (b) (6) days after receiving the second initial vaccination. The participant was not ill and had not been hospitalized in the last 6 months prior to his death**.** The cause of death and autopsy details were reported as unknown. The participant's family had agreed to provide the death

certificate once available, but the site was not able to reach them and there was no further response from the participant's family. The site confirmed that the autopsy report was not available and further information was unobtainable.

Clinical Reviewer Comment: Compared with the other participants who had unexplained death, this participant was younger, healthier, and without cardiovascular risk factors. However, there isn't a clear temporal relationship between vaccine administration and this participant's death.

Clinical Reviewer Comment Summarizing Unexplained Deaths: None of the 7 unexplained deaths that occurred in the post-crossover period were temporally related to vaccination. There was no clear pattern to any of the events that clearly indicate a safety signal. Because there is no comparator group, it is difficult to determine if there is a risk difference in this case. Overall, it is unlikely that these events are related to the Original Monovalent Vaccine.

Based on a numerical imbalance seen in atrial fibrillation including both serious and non-serious cases, atrial fibrillation was added to the Applicant's postmarketing surveillance which also includes myocarditis/ pericarditis, arrhythmia, and hemorrhagic and non-hemorrhagic stroke. Because the causes of death are unknown for 6 of the 7 cases, it is uncertain that the clinical trial data has captured all the potential safety signals that might have contributed to these fatal events. However, it is highly unlikely that these cases represent vaccine-related events.

- There was one case of ischemic stroke. The narrative is summarized below.
    - A 79-year-old White not Hispanic or Latino male participant with a history of chronic obstructive pulmonary disease, intermittent anemia, implanted bladder stimulator, and hypertension experienced an ischemic stroke 154 days after receiving the second of the Original Monovalent vaccine. The participant subsequently experienced a cerebral hemorrhage 159 days after the second vaccination dose because of stroke medications he received. The participant then experienced aspiration pneumonia (b) (6) days after receiving the second vaccine dose. Two days later, he died of complications from his stroke.

Clinical Reviewer Comment: There is no clear temporal relationship, which makes vaccine relatedness to this CVA event unlikely.

Booster Vaccination Period

The frequency and percentage of adverse events that resulted in death during the Booster Vaccination Period by System Organ Class (SOC) and PT are summarized in the table below.

Table 34. Frequency and Percentage of Adverse Events Resulting in Death During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Participants experiencing an event resulting in death	10 (<0.1)
Cardiac disorders	5 (<0.1)
Cardiac arrest	4 (<0.1)
Arrythmia	1 (<0.1)

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Gastrointestinal disorders	2 (<0.1)
Intestinal ischemia	1 (<0.1)[a]
Upper gastrointestinal hemorrhage	1 (<0.1)[a]
Infections and infestations	2 (<0.1)
Sepsis	1 (<0.1)
Septic shock	1 (<0.1)[1]
General disorders and administration site conditions	1 (<0.1)
Death	1 (<0.1)
Injury, poisoning and procedural complications	1 (<0.1)
Road traffic accident	1 (<0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (<0.1)
Esophageal adenocarcinoma stage IV	1 (<0.1)

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report Table 180, page 401
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Booster Safety Analysis Set who received the booster dose and completed at least 1 day of the reactogenicity diary for that dose; PT=preferred term
a. participant was included under the PTs of intestinal ischemia, upper gastrointestinal hemorrhage, and septic shock.

There were 10 (<0.1%) deaths in the Booster Period, and 4 had clear alternative etiologies including intestinal ischemia/ upper gastrointestinal hemorrhage/ septic shock, sepsis, road traffic accident, and esophageal adenocarcinoma stage IV. The remaining events are as follows:

- Cardiac Arrest occurred in 4 (<0.1%) participants. The details of these cases are as follows:
    - A 53-year-old male participant with a history of alcohol abuse and “alcohol withdrawal complication”, hypertension, sleep apnea, type II diabetes mellitus, chronic obstructive pulmonary disease, congestive cardiac failure, class III obesity, and tobacco use (half pack per day for 30 years) suffered cardiac arrest (b) (6) days after receiving the first booster Original Monovalent vaccination. Emergency Medical Services was called as the participant was found having a seizure. Upon arrival, they found him unresponsive but breathing; however, he became apneic and pulseless in the ambulance and was unable to be revived in the Emergency Department. The immediate cause of death was attributed to cardiac arrest, seizure, and alcohol withdrawal with delirium tremens. Toxicology screening and an autopsy were not performed. The participant was cremated. The principal investigator assessed the cardiac arrest as not related to the vaccine. Though there is a possible temporal relationship between vaccine administration and the cardiac arrest, there is also a very plausible medical explanation for this participant’s death. The contention that the cardiac arrest in this case was not related to the vaccine is reasonable.

Reviewer Comment: There was no temporal association to vaccine administration, and there is a clear alternative explanation for this participant’s death (alcohol withdrawal with delirium tremens), making vaccine relatedness unlikely.

    - A 61-year-old Black female participant with an extensive medical history including but not limited to hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, coronary angioplasty with multiple stent placements, mitral valve stenosis with prosthetic heart valve replacement, peripheral vascular disease with placement of multiple drug eluting stents, and cerebral artery occlusion with cerebral infarction suffered cardiac arrest 202 days after receiving the booster

Original Monovalent vaccination. The participant was successfully treated for bacterial endocarditis, and roughly 1 month later, she presented to the Emergency Department with bioprosthetic mitral valve thrombotic stenosis. She developed respiratory failure, was intubated, and was taken to the operating room emergently where she suffered cardiac arrest and was unable to be resuscitated.

Clinical Reviewer Comment: The principal investigator assessed the events of cardiac arrest, mitral valve stenosis, acute respiratory failure, and bacterial endocarditis as severe in intensity and not related to the study vaccine. Because there is no clear temporal association between the death and vaccine administration as well as a reasonable medical explanation for this participant's death, the principal investigator's conclusion that the cardiac arrest was not related to the vaccine is reasonable.

- A 44-year-old American Indian or Alaska Native male participant with a medical history significant for nicotine dependence and tobacco use, substance abuse, diabetes mellitus, high blood pressure, chronic alcohol dependence, and cirrhosis suffered cardiac arrest (b) (6) days after receiving the first booster Original Monovalent vaccination. He was found unresponsive on the floor of his residence with a Glasgow Coma Scale (GCS) of 3, a clear airway, absent breathing and pulses, fixed and dilated pupils (7 mm), skin that was jaundiced and cold to the touch, and multiple bruises and lacerations due to a previous fall. He was reported as "death on arrival" due to a Glasgow Coma Scale of 1. He was seen alive 3 hours before his death. An autopsy was ordered, but the report was not available. The death certificate listed the immediate cause of death as cardiac arrest with hepatic cirrhosis and alcoholic liver cirrhosis as underlying causes of death. The principal investigator assessed the event of cardiac arrest as severe in intensity and not related to the study vaccine.

Clinical Reviewer Comment: In this case, there is a temporal relationship between the cardiac arrest event and Original Monovalent administration. Myocardial infarction and arrhythmia leading to cardiac arrest are possible complications of end stage liver disease, which this participant appeared to have. However, due to the temporal relationship of the event to vaccine administration, the possibility of vaccine relatedness is unlikely but cannot be entirely excluded.

- A 36-year-old American Indian or Alaska Native female participant with no significant past medical history suffered cardiac arrest (b) (6) days after receiving the first booster vaccination. The participant collapsed at home. Emergency Medical Services was called, and the participant was taken to the Emergency Department and was later transferred via air to another hospital on the same day. The participant received CPR for about 30 minutes and was found to have severe anoxic brain injury. Laboratory data were significant for lactic acid of 19.2 mmol/L (reference range: 0.4-2.0), troponin of 94.60 pg/mL (reference range: 0.00-51.40), INR of 1.17 (reference range: 0.88-1.12), platelets of 119.0 thousand per cubic millimeter (reference range: 133.0-351.0), glucose of 330 mg/dL (reference range: 74.0-106.0), potassium of 2.4 mEq/L (reference range: 3.5-5.1), aspartate aminotransferase of 84 IU/L (reference range:15-37). An electrocardiogram showed atrial fibrillation with rapid ventricular response, atrial flutter 2:1, and atrioventricular conduction rate at 122. An echocardiogram showed global hypokinesis and complete akinesis of the apical segments. These findings were suggestive of stress-induced cardiomyopathy versus likely proximal left anterior descending artery disease. Computed tomography (CT) scans of the head and neck were unremarkable. CT angiogram of abdomen and pelvis was negative for PE, edema, infiltrate or acute appearing chest abnormalities; however, a large mass was seen in the left adrenal fossa

which was suspicious for adrenal neoplasm. The participant ultimately died of cardiac arrest. It was not known whether an autopsy was performed. The principal investigator assessed the event of cardiac arrest as severe in intensity and not related to the study vaccine.

Clinical Reviewer Comment: As documented, this was a young participant with no other medical history who sustained an anoxic brain injury secondary to a cardiac event and ultimately died of cardiac arrest, and even though there was not a strong temporal relationship, the possibility of vaccine involvement was considered. However, this clinical picture could also be consistent with an adrenocortical carcinoma which was functional and secreting aldosterone, which could have caused the hypokalemia. Cushing Syndrome symptoms can also be present in cases of adrenocortical carcinoma which could have explained the hyperglycemia. The hypokalemia could have precipitated an unstable cardiac arrhythmia that could have resulted in loss consciousness, asystole, hypoxia, and anoxic brain injury. Though not definitive, the findings of stress-induced cardiomyopathy on the echocardiogram provide further support for this hypothesis as does the finding of atrial fibrillation with rapid ventricular response seen on the electrocardiogram. Given the lack of a temporal relationship to vaccine administration and other medically plausible explanations for this participant's cardiac arrest and death, vaccine involvement is unlikely in this case.

- Arrhythmia occurred in 1 participant. The details of this case are as follows:
  - A 70-year-old Black or African American male with a history of angina, diabetes type-2, hypertension, chronic renal disease stage 4, gout, dyslipidemia, and neuropathy died of an arrhythmia at home (b) (6) days after receiving the first booster Original Monovalent vaccination. The participant's death certificate revealed the immediate cause of death as cardiac arrhythmia due to chronic renal disease stage 4, diabetes, and hypertension.

Clinical Reviewer Comment: While there was a temporal association between the cardiac arrest and vaccine administration, the participant had multiple risk factors for cardiac disease which may have resulted in a fatal cardiac event; therefore, the possibility of vaccine relatedness is unlikely but cannot be entirely excluded.

- Death without further explanation occurred in 1 participant. The details of this case are as follows:
  - A 44-year-old White not Hispanic or Latino female participant with a history spinal meningitis, hypertension, chronic migraines, lobectomy of brain, headaches, cholecystectomy, and cyst removal from her thyroid died (b) (6) days after receiving Original Monovalent as the first booster vaccination. The death was noted based on an obituary. Her sister confirmed her death was not related to COVID-19. The cause of death and a copy of the death certificate was verbally requested from the site; however, the site never heard back from her.

Clinical Reviewer Comment: The cause of death remained unknown, and it was unknown whether an autopsy was performed. There is no temporal association, and vaccine relatedness is unlikely.

Please see Section 6.1.12.5 for additional discussion of cardiac events.

6.1.12.4 Nonfatal Serious Adverse Events

Summary of Overall SAEs

The frequency and percentage of participants reporting SAEs by vaccine group and age group during the initial vaccination period for the Safety Analysis Set is presented in the table below.

Table 35. Frequency and Percentage of Participants Reporting SAEs During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Parameter	Original Monovalent n/N (%)	Placebo n/N (%)
Participants 18 to <65 years of age	--	--
Within 7 days of any dose	17/17255 (0.1)	13/8612 (0.2)
Within 28 days of any dose	69/17255 (0.4)	41/8612 (0.5)
Through data cutoff date	174/17255 (1.0)	90/8612 (1.0)
Participants ≥65 years of age	--	--
Within 7 days of any dose	5/2480 (0.2)	1/1235 (0.1)
Within 28 days of any dose	21/2480 (0.8)	8/1235 (0.6)
Through data cutoff date	54/2480 (2.2)	25/1235 (2.2)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Page 99, Table 58
Abbreviations: n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; SAE=serious adverse event.
Note: For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and date of data cutoff date (18 August 2022).

Reviewer Comment: There were twice as many participants ≥65 years of age who experienced an SAE compared with the 18 to <65 years of age group (2.2% vs 1.0%) through data cutoff. Furthermore, there are slightly higher percentages of SAEs that could have a temporal relationship to vaccine administration in participants ≥65 years of age compared with the 18 to <65 years of age group, for both the 7- and 28-day timepoints (0.2 and 0.8 percent compared with 0.1 and 0.4 percent). With that said, there are no imbalances in the percentage of participants who experienced SAEs in the vaccine and placebo groups. Therefore, the clinical significance of the higher percentages of participants aged ≥65 is uncertain. The percentages of participants with SAEs are low, and the safety profile is reassuring.

The frequency and percentage of participants reporting SAEs by vaccine group and age group during the Blinded Crossover Vaccination Period for the Safety Analysis Set is presented in the table below.

Table 36. Frequency and Percentage of Participants Reporting SAEs by Vaccine Group and Age Group During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Parameter	Placebo to Original Monovalent n/N (%)	Original Monovalent to Placebo n/N (%)
Participants 18 to <65 years of age	--	--
Within 7 days of any dose	7/5686 (0.1)	8/13576 (0.1)
Within 28 days of any dose	28/5686 (0.5)	54/13576 (0.4)
Through data cutoff date	117/5686 (2.1)	268/13576 (2.0)

Parameter	Placebo to Original Monovalent n/N (%)	Original Monovalent to Placebo n/N (%)
Participants ≥65 years of age	--	--
Within 7 days of any dose	1/730 (0.1)	2/1722 (0.1)
Within 28 days of any dose	7/730 (1.0)	21/1722 (1.2)
Through data cutoff date	47/730 (6.4)	96/1722 (5.6)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Page 102, Table 60
Abbreviations: n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; SAE=serious adverse event.
Note: Follow-up time is from first dose of crossover period to the earliest date of early termination and date of data cutoff date (18 August 2022).

Compared with the Initial Vaccination Period, there were higher percentages of participants with SAEs through the data cutoff date for both the Placebo to Original Monovalent and the Original Monovalent to Placebo groups in both the 18 to <65 (2.1% and 2.0%) and ≥65 years of age groups (6.4% and 5.6%). The percentage of participants with SAEs within the 7- and 28-day windows during Blinded Crossover Vaccination Period for both age subgroups in both the Placebo to Original Monovalent and the Original Monovalent to Placebo treatment arms were comparable with those seen at the same time points in the Initial Vaccination Period.

Reviewer Comment: The clinical significance of the higher percentages of SAEs in Blinded Crossover Period is not entirely clear. However, the percentages of participants with SAEs are low, and the safety profile is reassuring.

The frequency and percentage of participants reporting SAEs by vaccine group and age group during the Booster Vaccination Period for the Safety Analysis Set is presented in the table below.

Table 37. Frequency and Percentage of Participants Reporting SAEs by Vaccine Group and Age Group During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

Parameter	Original Monovalent Booster n/N (%)
Participants 18 to <65 years of age	--
Within 7 days of dose	11/11289 (0.10)
Within 28 days of dose	33/11289 (0.29)
Through data-cut date	156/11289 (1.38)
Participants ≥65 years of age	--
Within 7 days of dose	2/2064 (0.10)
Within 28 days of dose	13/2064 (0.63)
Through data-cut date	71/2064 (3.44)

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Page 105, Table 61
Abbreviations: n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; SAE=serious adverse event.
Note: Follow-up time is from first dose of crossover period to the earliest date of early termination and date of data cutoff date (18 August 2022).

Reviewer Comment: The percentages of SAEs were higher in individuals aged ≥65 years compared with individuals aged 18 to <65 years within 28 days of dose and through the data-cut date during the Booster Vaccination Period (0.63% and 3.44% compared with 0.29% and 1.38%, respectively). The percentages of SAEs in individuals aged ≥65 years and individuals aged 18 to <65 years through the data-cut date during the Booster Vaccination Period were comparable with those seen during the Initial Vaccination and Crossover Vaccination Periods.

Nonfatal SAEs

A summary of the frequency and percentage of SAEs by system organ class and preferred term for events reported for ≥3 participants within a vaccine group during the initial vaccination period (Safety Analysis Set) are presented in the table below.

Table 38. Frequency and Percentage of Serious Adverse Events Reported for ≥3 Participants Within a Vaccine Group During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Original Monovalent N=19735 E	Placebo N=9847 n (%)	Placebo N=9847 E
Participants experiencing any SAE	228 (1.2)	317	115 (1.2)	158
Infections and infestations	41 (0.2)	46	32 (0.3)	37
Appendicitis	6 (<0.1)	6	4 (<0.1)	4
Pneumonia	4 (<0.1)	4	4 (<0.1)	4
Appendicitis perforated	4 (<0.1)	4	1 (<0.1)	1
Pneumonia aspiration	4 (<0.1)	4	0	0
COVID-19 pneumonia	2 (<0.1)	2	10 (0.1)	10
Cardiac disorders	40 (0.2)	48	20 (0.2)	20
Atrial fibrillation	10 (<0.1)	10	2 (<0.1)	2
Myocardial infarction	6 (<0.1)	6	3 (<0.1)	3
Cardiac arrest	5 (<0.1)	5	4 (<0.1)	4
Cardiac failure congestive	4 (<0.1)	4	2 (<0.1)	2
Coronary artery disease	3 (<0.1)	3	0	0
Acute myocardial infarction	3 (<0.1)	3	3 (<0.1)	3
Injury, poisoning and procedural complications	27 (0.1)	30	16 (0.2)	17
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	27 (0.1)	27	7 (<0.1)	7
Prostate cancer	6 (<0.1)	6	1 (<0.1)	1
Breast cancer	3 (<0.1)	3	0	0
Nervous system disorders	23 (0.1)	24	10 (0.1)	10
Cerebrovascular accident	8 (<0.1)	8	1 (<0.1)	1
Syncope	2 (<0.1)	2	3 (<0.1)	3
Gastrointestinal disorders	20 (0.1)	23	6 (<0.1)	7
Respiratory, thoracic, and mediastinal disorders	18 (<0.1)	22	8 (<0.1)	8
Pulmonary embolism	6 (<0.1)	6	2 (<0.1)	2
Acute respiratory failure	4 (<0.1)	4	0	0
Chronic obstructive pulmonary disease	3 (<0.1)	4	1 (<0.1)	1
Hepatobiliary disorders	15 (<0.1)	19	2 (<0.1)	3
Cholecystitis acute	6 (<0.1)	6	1 (<0.1)	1
Cholelithiasis	4 (<0.1)	4	0	0
Cholecystitis	3 (<0.1)	3	1 (<0.1)	1
Bile duct stone	3 (<0.1)	3	1 (<0.1)	1
Psychiatric disorders	14 (<0.1)	15	8 (<0.1)	10
Depression	4 (<0.1)	4	0	0
Suicidal ideation	2 (<0.1)	2	4 (<0.1)	4
Vascular disorders	10 (<0.1)	11	6 (<0.1)	6
Renal and urinary disorders	10 (<0.1)	10	4 (<0.1)	4
Acute kidney injury	7 (<0.1)	7	2 (<0.1)	2
Nephrolithiasis	3 (<0.1)	3	2 (<0.1)	2

Primary System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Original Monovalent N=19735 E	Placebo N=9847 n (%)	Placebo N=9847 E
Musculoskeletal and connective tissue disorders	10 (<0.1)	10	3 (<0.1)	3
Intervertebral disc protrusion	3 (<0.1)	3	0	0
General disorders and administration site conditions	8 (<0.1)	8	5 (<0.1)	5
Metabolism and nutrition disorders	6 (<0.1)	6	6 (<0.1)	8
Pregnancy, puerperium, and perinatal conditions	8 (<0.1)	8	3 (<0.1)	5
Abortion spontaneous	5 (<0.1)	5	0	0
Blood and lymphatic system disorders	5 (<0.1)	5	1 (<0.1)	1

Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Table 59, pages 100-101
Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); E=number of events; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; SAE=serious adverse event.
Note: For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and date of data cutoff date (18 August 2022).

The most frequent SAEs in the Original Monovalent group during the Initial Vaccination Period were atrial fibrillation 10 (<0.1%) participants, cerebrovascular accident 8 (<0.1%) participants, and acute kidney injury 7 (<0.1%) participants.

> *Reviewer Comment: The percentages of participants with SAEs are low and comparable to the other safety periods. The percentages of participants who experienced an SAE during the Initial Vaccination Period were balanced between the vaccine and placebo groups (1.2%). No SAE occurred in more than 0.1% of vaccinated participants, and no imbalances were noted in the percentages of participants with SAEs in the vaccine and placebo groups.*

Atrial Fibrillation

A numerical imbalance in cases of serious atrial fibrillation was noted in the Initial Vaccination Period. There were 10 serious cases of atrial fibrillation in the vaccine group compared with 2 cases in the placebo group. In addition, there were 3 cases of non-serious atrial fibrillation in the vaccine group compared with 2 cases in the placebo group. Overall, there were 13 total cases of atrial fibrillation in the vaccine group compared with 4 cases in the placebo group. One of the participants with serious atrial fibrillation also had concurrent atrial flutter. Note that there was a 2:1 randomization scheme for the vaccine and placebo groups. This information is summarized in the SMQ analysis below.

Table 39. Atrial Fibrillation Cases, Adult Main Study 301

Arrhythmia	Original Monovalent N=19735 Events	Original Monovalent N=19735 n (%)	Placebo N=9847 Events	Placebo N=9847 n (%)	Original Monovalent vs Placebo RD (Per Hundred) (95% CI)	Original Monovalent vs Placebo RR (95% CI)	Original Monovalent vs Placebo OR (95% CI)	Original Monovalent vs Placebo p-value
Serious and non-serious atrial fibrillation	13	13 (0.07)	4	4 (0.04)	0.03 (-0.03, 0.08)	1.62 (0.53, 4.97)	1.62 (0.50, 6.83)	0.45
Serious atrial fibrillation	10	10 (0.05)	2	2 (0.02)	0.03 (-0.01, 0.07)	2.50 (0.55, 11.38)	2.50 (0.53, 23.43)	0.36

Source: Reviewer Table

Abbreviations: CI=confidence interval; OR=odds ratio; RD=risk difference; RR=relative risk, N=Safety Analysis Set; n=unique individuals with atrial fibrillation.

Clinical Reviewer Comment: This SMQ analysis of supraventricular tachyarrhythmias (SVT) shows that a total of 10 participants reported serious adverse events (SAEs) involving atrial fibrillation in the vaccine group (for a total of 11 SVT events, as 1 participant had both atrial fibrillation and atrial flutter) compared with 2 participants in the placebo group, with a 2:1 randomization scheme for the vaccine and placebo groups. The relative risk for the supraventricular tachyarrhythmia analysis was 2.50 (95% CI: 0.55, 11.38) with a p-value of 0.36. This constitutes a numerical imbalance with a non-statistically significant relative risk with a wide confidence interval. This reviewer's assessment is that this finding, though non-statistically significant, raises clinical suspicion for potential vaccine-relatedness of temporally associated cardiac events.

The narrative information for the serious cases of Atrial fibrillation is summarized below.

Table 40. Narrative Summaries of Atrial Fibrillation, Adult Main Study 301

Age, Sex, Medical History	Preferred Term	Time Since Last Study Vaccination (Excluding Days of Administration)	Resolution	Investigator's Causality Assessment	Review Team's Causality Assessment
65-year-old male, hypertension, coronary artery disease (CAD), triple bypass, congestive heart failure, paroxysmal atrial fibrillation	Atrial fibrillation with acute on chronic systolic congestive heart failure (CHF)	472 days Post-Dose (PD) 2	Yes	Not related	Not related
64-year-old male, CAD, stent, smoker, type 2 diabetes, hypertension, high cholesterol	New onset atrial fibrillation, elevated troponin due to CHF	52 days PD 2	Yes	Not related	Possibly related
56-year-old male, obesity, hypertension, hypothyroidism	Atrial fibrillation, Cerebrovascular accident (CVA), hypertension emergency	10 days PD 1	Yes	Not related	Possibly related
56-year-old female, hypertension, aflutter, alcohol use, cocaine	Atrial fibrillation, cardiac failure	7 days (CHF) and 21 days (Atrial fibrillation) PD 2	Yes	Not related	Possibly related
64-year-old male on hypertension, hyperlipidemia, former smoker	Atrial fibrillation with rapid ventricular response	21 days PD 1	Yes	Not related	Possibly related
50-year-old male hyperlipidemia	Atrial fibrillation, atrial flutter, PE, Cor Pulmonale acute, DVT	292 days PD2	No	Not related	Not related
60-year-old female, atrial fibrillation, hypothyroidism, hypertension, hyperlipidemia, smoker	"New Onset" Atrial fibrillation, CVA	(b) (6) days PD 2	No	Unknown	Unlikely related
65-year-old male hypertension, obesity, type 2 diabetes	Atrial fibrillation with no prior history	58 days PD 2	Yes	Not related	Unlikely related
47-year-old male obesity, hypertension, cardiac murmur	Atrial fibrillation, CHF	(b) (6) days PD 2	No	Not related	Possibly related
68-year-old with atrial fibrillation, patent foramen ovale, CVA, obesity	Atrial fibrillation	45 days PD 2	Yes	Not related	Unlikely related

Source: Reviewer table
Abbreviations: CAD=coronary artery disease; CHF=congestive heart failure; CVA=cerebrovascular accident; DVT=deep vein thrombosis; PD=post dose; PE=pulmonary embolism

All the participants with serious atrial fibrillation had a least one cardiac risk factor. Seven of these participants developed new onset atrial fibrillation. Two participants had concomitant stroke. Three of the atrial fibrillation cases presented are within a 30-day window after vaccination.

A table analyzing the serious and non-serous atrial fibrillation cases by a 55-year age cutoff (above age 55, the background rate of atrial fibrillation increases) and by a 30-day risk window is presented below.

Table 41. Non-Serious and Serious Atrial Fibrillation Cases, Adult Main Study 301

Atrial Fibrillation Events Within 30 Days After Vaccination	Pre-Crossover Original Monovalent n	Pre-Crossover Placebo n
All – 30 Days	6	2
All – Entire period	13	4
<55 years of age – 30 Days	2	0
<55 years of age – Entire period	4	0
≥55 years of age – 30 Days	4	2
≥55 years of age – Entire period	9	4

Source: Reviewer Table
Note: using latest dataset (2022)

Clinical Reviewer Comment: There were 2 cases of atrial fibrillation that occurred in a 30-day risk window in participants less than 55 years in the vaccine group compared with 0 participants in the placebo group. This number of cases doesn't exceed the background rate for atrial fibrillation in the lower risk population; however, a numerical imbalance between the vaccine and placebo groups is still noted. This imbalance has potential clinical relevance given the close temporal association to vaccination and the potential consequences of atrial fibrillation (e.g., increased risk of cerebrovascular accident and cardiac arrest).

Clinical Reviewer Summary Comment—Atrial Fibrillation: There is a numerical imbalance in cases of serious and non-serious atrial fibrillation that occurs during the initial vaccine period of Adult Main Study 301. There is a risk difference: there are two cases with a clear temporal relationship using a 30-day risk window; multiple cases of new onset atrial fibrillation; and two cases of atrial fibrillation that had concurrent stroke. The previously observed myocarditis/pericarditis safety finding associated with this vaccine and the observation that atrial fibrillation is commonly seen as a complication of myocarditis and pericarditis (Nso, et al.; 2021) suggest a biologically plausible mechanism for a pro-arrhythmic state associated with myocardial inflammation up to 30 days after vaccination. There is also at least 1 case report in the medical literature of an individual developing atrial fibrillation as a precursor to vaccine related myocarditis/ pericarditis (Scheuermeyer, et al., 2022). Therefore, there is sufficient evidence to conclude that atrial fibrillation may be a potential safety signal that warrants additional investigation. This reviewer recommends that atrial fibrillation be added to Section 6.2 of the USPI and to the Applicant's postmarketing surveillance studies, as postmarketing commitments.

Non-Hemorrhagic Stroke

A small numerical imbalance in cerebrovascular accident (CVA) was noted in the Initial Vaccination Period. There were 8 cases of CVA in the vaccine group compared with 1 case in the placebo group. During the safety review, it was noted that there were other preferred terms that were coded during the Initial Vaccination Period that pertained to stroke. To capture these

terms and analyze for imbalances, a Central Nervous System Vascular Disorders SMQ was used. This SMQ is presented below.

Table 42. Central Nervous System Vascular Disorders, Adult Main Study 301

High Level Group Term / High Level Term / Preferred Term	Original Monovalent N=19735 Number of Events/ Participants[a] (%)	Placebo N=9847 Number of Events/ Participants[a] (%)	Original Monovalent vs Placebo RD (Per Hundred) (95% CI)	Original Monovalent vs Placebo RR (95% CI)	Original Monovalent vs Placebo OR (95% CI)	Original Monovalent vs Placebo p-Value
Central nervous system vascular disorders	13 (0.07)	4 (0.04)	0.03 (-0.032, 0.08)	1.62 (0.53, 4.97)	1.62 (0.50, 6.83)	0.45
Central nervous system hemorrhages and cerebrovascular accidents	10 (0.05)	2 (0.02)	0.03 (-0.01, 0.07)	2.49 (0.55, 11.38)	2.50 (0.53, 23.43)	0.36
Cerebellar infarction	0	1 (0.01)	-0.01 (-0.03, 0.01)	0.17 (0.01, 4.08)	0.17 (0.01, 4.08)	0.33
Cerebral infarction	1 (0.01)	0	0.01 (0.00, 0.01)	1.50 (0.06, 36.74)	1.507 (0.06, 36.75)	1
Cerebrovascular accident	8 (0.04)	1 (0.01)	0.03 (0.00, 0.06)	3.99 (0.50, 31.91)	3.99 (0.54, 177.19)	0.29
Ischemic stroke	1 (0.01)	0	0.01 (0.00, 0.01)	1.50 (0.06, 36.74)	1.50 (0.06, 36.75)	1
Transient cerebrovascular events	2 (0.01)	1 (0.01)	0 (-0.02, 0.02)	1.00 (0.09, 11.00)	1.00 (0.05, 58.88)	1
Transient ischemic attack	2 (0.01)	1 (0.01)	0 (-0.02, 0.02)	1.00 (0.09, 11.00)	1.00 (0.05, 58.88)	1

Source: Reviewer table
Abbreviations: CI=confidence interval; OR=odds ratio; RD=risk difference; RR=relative risk
a. Number of events was equal to number of participants

Clinical Reviewer Comment: This SMQ analysis Central Nervous System Vascular Disorders shows that a total of 14 participants reported events in the vaccine group compared with 3 participants in the placebo group, with a 2:1 randomization scheme for vaccine and placebo groups. The preferred terms in the SMQ included cerebrovascular accident, cerebellar infarction, cerebral infarction, ischemic stroke, and TIA. The relative risk for Central Nervous System Vascular Disorders was 1.622.00 (95% CI: 0.50, 6.83) with a p-value of 0.451 To make this analysis more relevant, TIA was excluded. Therefore, the numbers of participants with preferred terms for non-hemorrhagic stroke were cerebrovascular accident, cerebellar infarction, cerebral infarction, ischemic stroke, resulting in 10 events in the vaccine group and 2 events in the placebo. This suggests a numerical imbalance and a small risk difference between the vaccine and placebo groups. This reviewer's assessment is that this finding, though not statistically significant, raises clinical suspicion for a potential safety signal for non-hemorrhagic stroke when considered in the context of the other safety data (i.e., a potential signal in atrial fibrillation, cases of atrial fibrillation with concomitant CVA, etc.). Hemorrhage and non-hemorrhagic stroke are currently part of the Applicant's postmarketing surveillance.

The narrative information for the serious cases of non-hemorrhagic stroke is summarized below.

Table 43. Narrative Summaries of Non-Hemorrhagic Stroke, Adult Main Study 301

Age, Sex, Medical History	Preferred Term	Time Since Last Study Vaccination Excluding Days of Administration (Study Vaccine)	Resolution	Investigator's Causality Assessment	Review Team's Causality Assessment
61-year-old male, hypertension (HTN) and left-hand nerve pain	Cerebellar infarction	8 days post-Dose (PD) 2 (Placebo)	Resolved	Not related	Placebo
72-year-old male, HTN, high cholesterol, prediabetes	Cerebral Infarction	38 days PD 2	Not documented	Not related	Possibly related
53-year-old male, no significant past medical history	Cerebrovascular accident, myocardial infarction	Roughly 60 days, not clearly specified	Resolved with sequelae	Not related	Unlikely related
49-year-old male, hypercholesterolemia, HTN, diabetes, obesity, smoker, prior myocardial infarction	Cerebrovascular accident	14 days PD 2	Resolved	Not related	Possibly related
73-year-old male, COPD, breast mass, HTN, hypercholesterolemia, BMI 29.2	Cerebrovascular accident	11 days PD 1	Resolved with sequalae	Not related	Possibly related
75-year-old female, HTN, coronary artery disease (CAD), AD, hypothyroidism	Cerebrovascular accident	(b) (6) days PD 2	The participant died	Not related	Possibly related
59-year-old male, HIV, left parietal stroke, cerebellar stroke, coronary artery disease (CAD), smoker, drug use	Cerebrovascular accident bilateral strokes "likely embolic", aortic root enlargement	83 days PD2	Resolved with sequelae	Not related	Unlikely related
56-year-old female, obesity, hypertension, no prior history of atrial fibrillation	Cerebrovascular accident and atrial fibrillation (both coded), hypertensive emergency	10 days PD 1	Resolved	Not related	Possibly related

Age, Sex, Medical History	Preferred Term	Time Since Last Study Vaccination Excluding Days of Administration (Study Vaccine)	Resolution	Investigator's Causality Assessment	Review Team's Causality Assessment
60-year-old female, atrial fibrillation, hypothyroidism, hyperlipidemia, smoker	Cerebrovascular accident and atrial fibrillation	82 days PD 2	Resolved	Not related	Unlikely related
44-year-old female, no medical history	Cerebrovascular accident	266 days PD 2 (placebo)	Resolving	Not related	Placebo
66-year-old female, hyperlipidemia, tested positive for COVID-19	Cerebrovascular accident	318 days PD 2	Resolving	Not related	Unlikely related
52-year-old female, HTN, hyperlipidemia, hemorrhagic stroke, obesity	Ischemic stroke	31 days PD 1	Recovered/ Resolved	Not related	Possibly related

Source: Reviewer table
Abbreviations: BMI=body mass index; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019; HIV=human immunodeficiency virus; HTN=hypertension; PD=post-dose

Except for 2 participants, all the participants with non-hemorrhagic stroke had at least one risk factor for stroke. Two participants had atrial fibrillation. Three of the atrial fibrillation cases presented are within a 30-day window after vaccination, with one participant being a near miss (38 days after vaccination).

A table analyzing the CVA cases by a 30-day risk window is presented below.

Table 44. Frequency and Percentage of Non- Hemorrhagic Stroke Cases in Participants <55 Years of Age Occurring Within a 30-Day Risk Window or Entire Period, Adult Main Study 301

Observation Period	Pre-Crossover (2:1 Randomization) Original Monovalent N=19735 n (%)	Pre-Crossover (2:1 Randomization) Placebo N=9847 n (%)
30-Day Risk Window	3 (0.02)	1 (0.01)
Entire Period[a]	10 (0.05)	2 (0.02)

Source: Reviewer Table
a. (definition of Entire Period)
Note: using latest dataset (2022)

Clinical Reviewer Comment: There were 3 cases of non-hemorrhagic stroke that occurred in a 30-day risk window in the vaccine group compared with 1 participant in the placebo group. This number of cases doesn't exceed the background rate for cerebrovascular accident in the overall population; however, a numerical imbalance between the vaccine and placebo groups is still noted. This imbalance has potential clinical relevance as it coincides with a potential atrial fibrillation signal.

Clinical Reviewer Summary Comment—Non-Hemorrhagic Stroke: There is a numerical imbalance in cases of non-hemorrhagic stroke that occurs during the initial vaccine period of Adult Study 301. There is a small risk difference, a small number of X cases with a clear temporal relationship using a 30-day risk window, and two cases of atrial fibrillation that involved concurrent stroke. Given the potential for atrial fibrillation (considered a potential safety signal) to cause embolic events as a biologically plausible mechanism for vaccine relatedness, there is sufficient evidence to conclude that non-hemorrhagic stroke may be a potential safety signal that warrants further investigation. It is already included in the Applicant's postmarketing surveillance.

The most frequent SAEs in the placebo group during the Initial Vaccination Period were COVID-19 pneumonia 8 (0.1%) participants, appendicitis, pneumonia, cardiac arrest, and suicidal ideation 4 (<0.1%) participants, and COVID-19 3 (<0.1%) participants. The frequency and percentage of related SAEs (per the Investigator) in the Pre-Crossover Period by SOC and PT are presented in the table below.

Table 45. Frequency and Percentage of Related SAEs After First Vaccination, Pre-Crossover, Adult Main Study 301

System Organ Class Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Blood and lymphatic system disorders	1 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.0)	0 (0.0)
Cardiac disorders	1 (0.0)	2 (0.0)
Cardiac failure congestive	1 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.0)
Myopericarditis	0 (0.0)	1 (0.0)

System Organ Class Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Endocrine disorders	1 (0.0)	0 (0.0)
Basedow's disease	1 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (0.0)
Pneumonia	0 (0.0)	1 (0.0)
Septic shock	0 (0.0)	1 (0.0)
Nervous system disorders	2 (0.0)	0 (0.0)
Headache	1 (0.0)	0 (0.0)
Nervous system disorder	1 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.0)
Acute kidney injury	0 (0.0)	1 (0.0)
Skin and subcutaneous tissue disorders	1 (0.0)	0 (0.0)
Angioedema	1 (0.0)	0 (0.0)

Source: Reviewer Table

The related serious adverse events are summarized in the table below.

Table 46. Serious Adverse Events Considered Related by Investigator in the Pre-Crossover Period, Safety Analysis Set, Adult Main Study 301

Investigational Product	Serious Adverse Event	Onset (Days After Vaccination)[a]	Age (Years)/Sex Risk Factors	Resolution	Related (Per Novavax)
Original Monovalent	Headache	Day 45 (PD2)	53/F History of migraines	Recovered/ Resolved	No
Original Monovalent	Angioedema	Day 5 (PD1)	32/F History of penicillin allergy. Urticarial eruption which progressed the following day to diffuse rash with swelling of lower lips, tongue, and periorbital area. Resolved following treatment with epinephrine, dexamethasone, diphenhydramine, and famotidine. Concurrent urinary tract infection, concomitant medication Macrobid	Recovered/ Resolved	Yes
Original Monovalent	Basedow's disease	Day 29 (PD2)	39/F Baseline serum, prior to vaccination, positive for elevated thyroid stimulating immunoglobin	Not recovered/ Not resolved	No
Original Monovalent	Thrombocytopenia	Day 32 (PD2)	63/M Hypertension, concomitant use of losartan. Laboratory testing positive for Losartan immunoglobin G platelet antibody	Recovering/ Resolving	No
Original Monovalent	Nervous system disorder	Day 2 (PD2)	55/M Unilateral distal left lower extremity (LLE) peripheral neuropathy, acute left peroneal nerve palsy, and acute left foot drop. Recent physical assault and alcohol intoxication.	Recovering/ Resolving	Yes

Investigational Product	Serious Adverse Event	Onset (Days After Vaccination)[a]	Age (Years)/Sex Risk Factors	Resolution	Related (Per Novavax)
VX-CoV2373	Congestive Heart Failure	Day 46 (PD2)	38/F presented to the emergency room with complaints of a 4-day history of upper abdominal pain and chest pain. Troponin of 0.31 ng/mL and less than 0.03 ng/mL (reference range: less than 0.05), brain natriuretic peptide (BNP) of 785 pg/mL (reference range: 0-47). An ultrasound of the gallbladder showed fatty infiltration of liver, cholelithiasis, and no evidence of acute cholecystitis. The common bile duct (CBD) was slightly dilated and measured 7 mm in diameter and distal obstruction was suspected. A magnetic resonance cholangiopancreatography (MRCP) with contrast showed cholelithiasis with enhancement of the wall of the gallbladder which may relate to acute cholecystitis and no pericholecystic fluid was seen. A MRCP without contrast showed choledocholithiasis, common duct diameter was 6 mm with trace intrahepatic duct dilatation. Risk factors for congestive heart failure included obesity (BMI of 31.2 kg/m^2), tobacco use (1 pack of cigarettes per week), and concomitant use of phentermine, a sympathomimetic known to cause cardiac events. Per the narrative, baseline CHF was not entirely explained.	Recovered/ Resolved	No

Source: Reviewer Table
Abbreviations: F=female; M=male; PD1=post-Dose 1; PD2=post-Dose 2
a. Day of onset post last vaccination (most recent vaccination number).

Based on the above table, the following conclusions have been drawn from the data analyzed:

- This reviewer's opinion is that the event of angioedema is considered potentially related to Original Monovalent due to the temporal association (angioedema will be addressed in the USPI).
- The event of unilateral localized peroneal nerve injury is unlikely to be related based on plausible alternative etiology (trauma) and an implausible biological mechanism.
- The event of thrombocytopenia is unlikely to be related based on a plausible alternative etiology (losartan-induced).
- Headache and nervous system disorder are unlikely to have been caused by the vaccine due to plausible alternative etiologies.

One participant developed congestive heart failure as a related SAE. The narrative is summarized as follows:

- A 38-year-old Black or African American female with a history tobacco abuse and a prior appendectomy presented to the emergency department with symptoms of upper abdominal and chest pain 46 days after receiving the second initial Original Monovalent vaccination. She was found to have baseline congestive heart failure as well as cholelithiasis and choledocholithiasis (troponin of 0.31 ng/mL (reference range: less than 0.05), brain natriuretic peptide (BNP) of 785 pg/mL (reference range: 0-47). She underwent an endoscopic retrograde cholangiopancreatography with stent placement and removal of a 6 mm stone in the common bile duct and a cholecystectomy under general anesthesia with no blood loss. Post procedure, she experienced chest pain, difficulty in breathing, shortness of breath, severe pain generalized and abdominal, low ejection fraction of 25%, pneumonia, chronic hypersensitivity pneumonitis (non-serious), acute pulmonary edema, gallstones, abdominal tenderness, normal sinus rhythm with sinus arrhythmia, and aspiration pneumonia. Post laparoscopic cholecystectomy, she experienced non-ischemic cardiomyopathy secondary to procedural anesthesia and cardiac complications post cholecystectomy. An echocardiogram revealed low ejection fraction of 25-30%, stage II left ventricular diastolic function, slight left ventricular dilation, and wall motion and contractility were within normal limits. A chest x-ray showed new bilateral peri-hilar opacities and she was diagnosed with congestive heart failure. Treatment included amoxicillin-clavulanate, aspirin, lactobacillus acidophilus and bulgaricus, metoprolol succinate, and oxycodone. The participant was discharged from the hospital and had medical management and outpatient follow-up; the events of cardiac failure congestive, acute pulmonary edema, pneumonia aspiration, cardiomyopathy, and cardiac function disturbance postoperative were considered resolved.
- The Principal Investigator assessed the events of cholelithiasis, bile duct stone, acute pulmonary edema, pneumonia aspiration, and cardiomyopathy as moderate in intensity, the events of cardiac failure congestive and cardiac function disturbance postoperative as severe in intensity, the event of cardiac failure congestive as related to the study vaccine, and the events of cholelithiasis, bile duct stone, acute pulmonary edema, pneumonia aspiration, cardiomyopathy, and cardiac function disturbance postoperative as not related to the study vaccine. **In the opinion of the Principal Investigator, the causality for was cardiac failure congestive marked as related because the event occurred 46 days after the second initial vaccination, which was felt to be a temporal relationship and could not conclude for certain that the vaccination did not add to the causality. The Applicant assessed the events of cardiac failure**

congestive as not related to the study vaccine.

Reviewer Comment: This reviewer agrees with the Investigator that the baseline congestive heart failure in this case had a temporal relationship to vaccine administration such that vaccine relatedness cannot be entirely excluded. Though there are no imbalances between participants with cardiac SAEs in the vaccine and placebo groups, this is still a concerning case given the participant's age and temporal relationship.

The Applicant stated that the baseline congestive heart failure was unrelated to the vaccine and listed obesity, tobacco abuse, and phentermine as risk factors that could have contributed to this participant's baseline congestive heart failure. Congestive heart failure is not a known side effect of phentermine, and it is unlikely that tobacco abuse and Grade 1 obesity contributed to a decompensation in this participant's cardiac function without another underlying cause. This reviewer does not agree with the Applicant's assessment of the participant's risk factors provide an alternative explanation for the baseline congestive heart failure.

There were 5 thromboembolic events, not considered by either the Investigator or the Applicant to be related to the study vaccine, which require further comment. They are as follows:

- A 56-year-old female participant with a history of obesity, coronary artery disease, hypertension, and hyperlipidemia reported symptoms of chest pain 2 days post-Dose 2 of Original Monovalent. She was diagnosed with non-ST elevated myocardial infarction (NSTEMI). Relevant laboratory test results included platelet count of 274 (units and reference range not provided) and troponin levels of 4.570 and 5.770 (reference range: 0-0.4 ng/mL). A cardiac catheterization was performed and drug-eluting stents to the circumflex and large obtuse marginal artery were placed.
- A 58-year-old male participant with a history of obesity (BMI 41 kg/m^2), high cholesterol, diabetes, and hypertension experienced an anterolateral ST elevation myocardial infarction approximately 45 minutes post-Dose 2 of Original Monovalent. Troponin I was normal with a result of less than 0.015 ng/mL (reference range: 0-0.045). The participant underwent a successful balloon angioplasty of the first diagonal branch, with stent placement.
- An 83-year-old male participant with a history of myocardial infarction, chronic bilateral lower extremity DVTs with inferior vena cava filter placement, hypertension, Type 2 diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, Alzheimer's disease, and dyslipidemia presented with respiratory distress and peripheral edema 2 days post-Dose 1 of Original Monovalent. The platelet count was 134 K/mm^3. A CTA of the chest with contrast showed right lower lobar and segmental pulmonary emboli, duplex ultrasound of the bilateral lower extremities showed bilateral DVTs, and echocardiogram revealed an ejection fraction of 35-45% and severely dilated left atrium. Acute on chronic decompensated systolic congestive heart failure exacerbation, acute respiratory failure, and pulmonary embolism were diagnosed. Anti-coagulation was initiated, and the participant was discharged home. He subsequently experienced recurrent exacerbations of congestive heart failure.
- A 54-year-old male participant with a history of obesity, primary thrombophilia, recurrent DVT left leg and recurrent pulmonary embolism from 2012, non-compliance issues and morbid obesity since 2012, left femoral stent placement in 2012, and stents on proximal left lower extremities presented with leg and hip pain 4 days post-Dose 1 of Original Monovalent and was diagnosed with an acute DVT and pulmonary embolism.

- A 44-year-old male participant with a history of obesity, hypertriglyceridemia, proximal right coronary artery stenosis with stent placement presented with palpitations (heart rate increased to 140 beats per minute) and chest and left arm pain on the day of the first dose of Original Monovalent (following a caffeinated beverage and exercise). Electrocardiogram was consistent with sinus tachycardia with a rate of 130 without sinus ischemic changes, and echocardiogram was normal, and the troponin was abnormal at 25 ng/L (normal: <20). The tachycardia and elevated troponin resolved overnight.

Clinical Reviewer Comment: In considering the temporal relationship with vaccination, the reviewer notes that all 5 thromboembolic events occurred within 4 days of vaccination and two of the thromboembolic events on the same day as vaccination (i.e., a 44-year-old male with a history of cardia disease and a 58-year-old male with cardiac risk factors who experienced a myocardial infarction approximately 45 minutes post-Dose 2. For context, there were no imbalances between the vaccine and placebo groups for any cardiac-related preferred term during the initial vaccination period. In addition, there were cases of temporally associated cardiac events, some fatal, that occurred in the placebo group. Nonetheless, because two thromboembolic cases occurred on the same day of vaccination, the clinical team had increased clinical suspicion that the numerical imbalances seen during the Initial Vaccination Period suggested a biologically plausible mechanism for a pro-arrhythmic state associated with myocardial inflammation, as discussed in the atrial fibrillation analysis above.

A summary of the frequency and percentage of SAEs by System Organ Class and Preferred Term for events reported for ≥3 participants within a vaccine group during the blinded crossover vaccination period for the Safety Analysis Set is presented in the table below.

Table 47. Frequency and Percentage of Serious Adverse Events Reported for ≥3 Participants Within a Vaccine Group During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Placebo to Original Monovalent N=6416 Events	Original Monovalent to Placebo N=1529 n (%)	Original Monovalent to Placebo N=1529 Events
Participants experiencing any SAE	164 (2.6)	249	364 (2.4)	557
Infections and infestations	50 (0.8)	58	90 (0.6)	111
COVID-19 pneumonia	13 (0.2)	13	22 (0.1)	22
Pneumonia	7 (0.1)	7	10 (<0.1)	10
Cellulitis	6 (<0.1)	6	7 (<0.1)	7
Appendicitis	2 (<0.1)	2	9 (<0.1)	9
Urinary tract infection	2 (<0.1)	2	3 (<0.1)	3
Sepsis	1 (<0.1)	1	8 (<0.1)	8
Diverticulitis	1 (<0.1)	1	4 (<0.1)	4
Osteomyelitis	1 (<0.1)	1	4 (<0.1)	4

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Placebo to Original Monovalent N=6416 Events	Original Monovalent to Placebo N=1529 n (%)	Original Monovalent to Placebo N=1529 Events
Cardiac disorders	25 (0.4)	30	50 (0.3)	65
Acute myocardial infarction	7 (0.1)	7	7 (<0.1)	7
Atrial fibrillation	6 (<0.1)	6	10 (<0.1)	12
Coronary artery disease	3 (<0.1)	3	3 (<0.1)	4
Myocardial infarction	2 (<0.1)	2	6 (<0.1)	6
Cardiac failure congestive	2 (<0.1)	2	5 (<0.1)	5
Acute coronary syndrome	1 (<0.1)	1	3 (<0.1)	3
Angina unstable	0	0	3 (<0.1)	3
Bradycardia	0	0	3 (<0.1)	3
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	22 (0.3)	23	40 (0.3)	40
Prostate cancer	3 (<0.1)	3	4 (<0.1)	4
Invasive ductal breast carcinoma	2 (<0.1)	2	3 (<0.1)	3
Uterine leiomyoma	1 (<0.1)	1	3 (<0.1)	3
Colon cancer	0	0	3 (<0.1)	3
Respiratory, thoracic, and mediastinal disorders	20 (0.3)	23	40 (0.3)	54
Pulmonary embolism	8 (0.1)	8	9 (<0.1)	10
Chronic obstructive pulmonary disease	3 (<0.1)	3	10 (<0.1)	15
Acute respiratory failure	3 (<0.1)	3	9 (<0.1)	10
Respiratory failure	2 (<0.1)	2	3 (<0.1)	3
Hypoxia	1 (<0.1)	1	3 (<0.1)	3
Asthma	0	0	3 (<0.1)	3
Hepatobiliary disorders	15 (0.2)	16	12 (<0.1)	14
Cholecystitis chronic	4 (<0.1)	4	1 (<0.1)	1
Cholecystitis acute	3 (<0.1)	3	6 (<0.1)	6
Cholecystitis	3 (<0.1)	3	1 (<0.1)	1
Nervous system disorders	14 (0.2)	17	32 (0.2)	35
Seizure	1 (<0.1)	1	4 (<0.1)	4
Cerebrovascular accident	1 (<0.1)	1	5 (<0.1)	5
Syncope	0	0	5 (<0.1)	5
Injury, poisoning, and procedural complications	12 (0.2)	8	35 (0.2)	47
Road traffic accident	2 (<0.1)	2	4 (<0.1)	4
Rib fracture	1 (<0.1)	1	3 (<0.1)	3
Psychiatric disorders	12 (0.2)	24	22 (0.1)	35
Suicidal ideation	2 (<0.1)	3	7 (<0.1)	7
Depression	1 (<0.1)	1	6 (<0.1)	6
Anxiety	1 (<0.1)	3	4 (<0.1)	4
Alcohol withdrawal syndrome	1 (<0.1)	1	3 (<0.1)	3
Renal and urinary disorders	7 (0.1)	9	19 (0.1)	24
Acute kidney injury	3 (<0.1)	5	9 (<0.1)	9
Nephrolithiasis	3 (<0.1)	3	5 (<0.1)	5
Chronic kidney disease	0	0	3 (<0.1)	3
Hydronephrosis	0	0	3 (<0.1)	3
Vascular disorders	7 (0.1)	7	13 (<0.1)	16
Deep vein thrombosis	1 (<0.1)	1	5 (<0.1)	6

Primary System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Placebo to Original Monovalent N=6416 Events	Original Monovalent to Placebo N=1529 n (%)	Original Monovalent to Placebo N=1529 Events
Gastrointestinal disorders	6 (<0.1)	7	26 (0.2)	30
Gastrointestinal hemorrhage	2 (<0.1)	2	4 (<0.1)	4
Intestinal obstruction	0	0	4 (<0.1)	4
Small intestinal obstruction	0	0	3 (<0.1)	3
Metabolism and nutrition disorders	5 (<0.1)	6	15 (<0.1)	16
Dehydration	2 (<0.1)	2	3 (<0.1)	3
Diabetic ketoacidosis	1 (<0.1)	0	3 (<0.1)	3
General disorders and administration site conditions	4 (<0.1)	4	14 (<0.1)	15
Death	0	0	7 (<0.1)	7
Musculoskeletal and connective tissue disorders	3 (<0.1)	3	22 (0.1)	23
Osteoarthritis	1 (<0.1)	1	5 (<0.1)	6
Ear and labyrinth disorders	3 (<0.1)	3	1 (<0.1)	1
Vertigo	3 (<0.1)	3	1 (<0.1)	1
Reproductive system and breast disorders	2 (<0.1)	2	6 (<0.1)	6
Pregnancy, puerperium, and perinatal conditions	2 (<0.1)	2	11 (<0.1)	11
Abortion spontaneous	2 (<0.1)	2	7 (<0.1)	7
Blood and lymphatic system disorders	0	0	5 (<0.1)	5
Anemia	0	0	3 (<0.1)	3
Endocrine disorders	0	0	4 (<0.1)	4

Source: Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Table 61, pages 102-105
MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: Follow-up time is from first dose of crossover period to the earliest date of early termination and date of data cutoff date (18 August 2022).

Clinical Reviewer Comment: The overall percentages of participants who experienced an SAE during the Blinded Crossover period were balanced between the Placebo to Original Monovalent and Original Monovalent to Placebo groups (2.6% vs. 2.4%, respectively). No SAE occurred in more than 0.1% of vaccinated participants, suggesting that the safety profile of Original Monovalent during the Post-Crossover period was comparable to the Initial Vaccination Period in regard to SAEs. The most frequent SAEs in the Placebo to Original Monovalent group during the Post-Crossover Period were COVID-19 pneumonia 12 (0.1%) participants, pulmonary embolism 8 (<0.1%) participants, and COVID-19, pneumonia, and acute myocardial infarction 7 (<0.1%) participants. The most frequent SAEs in the Original Monovalent to placebo group during the Post-Crossover Period were COVID-19 pneumonia 20 (0.1%) participants, COVID-19 12 (<0.1%) participants, and pneumonia, atrial fibrillation, and chronic obstructive pulmonary disease 10 (<0.1%) participants.

The frequency and percentage of related SAEs (per the Investigator) in the Post-Crossover period by SOC and PT are presented in the tables below.

Table 48. Frequency and Percentage of Related SAEs After Second Vaccination, Post-Crossover, Adult Main Study 301

System Organ Class Preferred Term	Original Monovalent N=6416 n (%)	Placebo N=15298 n (%)
Gastrointestinal disorders	0 (0.0)	1 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.0)
Hepatobiliary disorders	1 (0.0)	0 (0.0)
Biliary dyskinesia	1 (0.0)	0 (0.0)
Cholecystitis chronic	1 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0 (0.0)	1 (0.0)
Lymphoma	0 (0.0)	1 (0.0)
Nervous system disorders	0 (0.0)	2 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.0)
Optic neuritis	0 (0.0)	1 (0.0)
Respiratory, thoracic, and mediastinal disorders	1 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.0)	0 (0.0)

Source: Reviewer table

Table 49. Serious Adverse Events Considered Related by Investigator in the Post-Crossover Period, Safety Analysis Set, Adult Main Study 301

Investigational Product	Serious Adverse Event	Onset (Day After Vaccination)[a]	Age (Years)/Sex Risk Factors	Resolution	Related (Per Applicant)
Placebo to Original Monovalent	Biliary dyskinesia, Cholecystitis chronic	Day 24, 2nd Crossover Dose	24/M History of chronic abdominal pain, anxiety, and depression; diagnosed with biliary dyskinesia by a hepatobiliary iminodiacetic acid scan. Participant underwent laparoscopic cholecystectomy. Pathology findings consistent with mild chronic cholecystitis Per the Investigator "There was a possibility that the study vaccine aggravated the participant's existing gallbladder issues leading to cholecystectomy."	Resolved	No
Placebo to Original Monovalent	Pulmonary embolism	Day 6, 2nd Crossover Dose	40/F History of migraines, obesity (calculated BMI of 36.7 kg/m^2), and oral contraceptive use. Diagnosed with pulmonary embolism, D-dimer of 1.26 µg/ml, (reference range: less than 0.54), positive CT angiogram. Treated with IV heparin and discharged on Eliquis. "The Principal Investigator provided rationale for the causal relationship due to the timing of the event and the participant having had no history of long-standing clots blood clots in the legs, deep vein thrombosis, or pulmonary embolism." Obesity and oral contraceptives could have precipitated this event per the Applicant	Resolved	No
Original Monovalent to Placebo	Acute Pancreatitis	Day 129, 2nd Initial Dose	67/F History of depression, anxiety, gastroesophageal reflux disease, Nissen fundoplication, obesity, obstructive sleep apnea, cholecystectomy, deep vein thrombosis. Hospitalized with acute pancreatitis and given nothing by mouth. Abdominal CT scan revealed resolving acute pancreatitis. Laboratory tests, including lipase, triglycerides, liver function tests, and white cell count were within normal limits during the hospital course. Investigator rationale not clearly provided. There is no clear biologic plausibility (an abnormal CT scan with normal laboratory studies).	Resolved	No

Investigational Product	Serious Adverse Event	Onset (Day After Vaccination)[a]	Age (Years)/Sex Risk Factors	Resolution	Related (Per Applicant)
Original Monovalent to Placebo	Lymphoma	Day 118, 2nd Initial Dose	73/M History of benign essential hypertension, male erectile disorder, allergic rhinitis, and right groin mass. The participant developed a right groin mass that he did not report during the first and second initial vaccination visits. The mass was present at randomization, but he was vaccinated anyway. A right superficial inguinofemoral lymphadenectomy pathology showed an abnormal CD10 positive B-cell lymphoma, grade 3A follicular lymphoma, follicular pattern. The mass was present prior to vaccination per the Applicant which makes vaccine relatedness less biologically plausible.	Not resolved	No
Original Monovalent to Placebo	Cerebrovascular Accident	Day 73, 2nd Initial Dose	57/M History of post-traumatic stress disorder. A CT angiogram (CTA) showed dissection of the right intracranial portion (V4) of the vertebral artery with an intramural hematoma. Magnetic resonance imaging showed an acute dissection of the right vertebral artery with acute/subacute ischemic infarcts of the right posterior medulla, vermis, and medial cerebellum. Investigator rationale for causality was that this was an inflammatory event that occurred two weeks post-injection event within the window period of reactogenicity. This rationale is problematic as the participant received the placebo at 2 weeks.	Resolved	No
Original Monovalent to Placebo	Optic Neuritis	Day 104, 2nd Initial Dose	65/M History of congenital spinal fusion at C2 and C3, cervical pain, high cholesterol, and high blood pressure. Serum screening for antinuclear antibodies was positive for antibodies; pattern was DFS70 and titer was 1:80 (reference range: antibodies not present). The participant was diagnosed with left optic neuritis based on specialist consult and imaging tests. Relatedness was based on a temporal relationship to “blinded vaccine administration” which was the placebo dose. There is not a clear temporal relationship to vaccine administration (104 days from last vaccine dose).	Resolved	No

Source: Reviewer Table
Abbreviations: CT=computed tomography; F=female; M=malea. Day of onset post last vaccination (most recent vaccination number)

Clinical Reviewer Comment: Of the SAEs that were designated as related by the Investigator, only one had a biologically plausible and temporally associated event (cholecystitis chronic and biliary dyskinesia). Overall, there were no imbalances seen in biliary disorders in the Adult Main Study 301 safety database. The clinical significance of this potentially related case of cholecystitis chronic and biliary dyskinesia is unclear.

The frequency and percentage of SAEs reported for ≥3 participants during the booster vaccination period for the Booster Safety Analysis Set are presented in the table below.

Table 50. Frequency and Percentage of SAEs Reported for ≥3 Participants During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)	Original Monovalent Booster N=13353 Events
Participants experiencing any SAE	227 (1.7)	365
Infections and infestations	57 (0.4)	87
Pneumonia	10 (<0.1)	12
Sepsis	10 (<0.1)	11
Cellulitis	7 (<0.1)	7
Appendicitis	4 (<0.1)	4
COVID-19 pneumonia	3 (<0.1)	3
Urosepsis	3 (<0.1)	3
Cardiac disorders	31 (0.2)	42
Atrial fibrillation	6 (<0.1)	6
Coronary artery disease	5 (<0.1)	5
Cardiac arrest	4 (<0.1)	4
Acute myocardial infarction	3 (<0.1)	5
Angina pectoris	3 (<0.1)	3
Cardiac failure congestive	3 (<0.1)	3
Nervous system disorders	29 (0.2)	35
Cerebrovascular accident	6 (<0.1)	6
Ischemic stroke	4 (<0.1)	5
Transient ischemic attack	3 (<0.1)	3
Respiratory, thoracic, and mediastinal disorders	26 (0.2)	34
Acute respiratory failure	9 (<0.1)	11
Pulmonary embolism	7 (<0.1)	7
Chronic obstructive pulmonary disease	4 (<0.1)	5
Dyspnea	3 (<0.1)	3
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	22 (0.2)	22
Breast cancer	3 (<0.1)	3
Invasive ductal breast carcinoma	3 (<0.1)	3
Gastrointestinal disorders	20 (0.1)	22
Injury, poisoning and procedural complications	15 (0.1)	26
Fall	3 (<0.1)	3
Psychiatric disorders	14 (0.1)	15
Major depression	4 (<0.1)	4
Vascular disorders	11 (<0.1)	13
General disorders and administration site conditions	11 (<0.1)	12
Chest pain	4 (<0.1)	5
Musculoskeletal and connective tissue disorders	10 (<0.1)	11
Back pain	4 (<0.1)	4

Primary System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)	Original Monovalent Booster N=13353 Events
Metabolism and nutrition disorders	8 (<0.1)	9
Renal and urinary disorders	7 (<0.1)	7
Acute kidney injury	4 (<0.1)	4
Nephrolithiasis	3 (<0.1)	3
Hepatobiliary disorders[a]	7 (<0.1)	8
Cholecystitis acute[a]	3 (<0.1)	3
Blood and lymphatic system disorders	6 (<0.1)	7
Anemia	6 (<0.1)	6
Skin and spontaneous tissue disorders	4 (<0.1)	4
Investigations	3 (<0.1)	3

Source: Source: eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Table 63, pages 106-107
Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Booster Safety Analysis Set; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: For participants who did not crossover, their follow-up time is from first dose to the earliest date of early termination and date of data cutoff date (18 August 2022).
a. Excluded by error in the original CSR.

Clinical Reviewer Comment: The overall percentage of participants who experienced an SAE during the Booster Period was 1.7%. No SAE occurred in more than 0.1% of participants during the Booster Period, and the percentages of SAEs during the booster period was comparable with those seen during the pre- and post-crossover periods. The most frequent SAEs during the Booster Period were pneumonia and sepsis 10 (0.1%) participants, acute respiratory failure 9 (<0.1%) participants, and cellulitis and pulmonary embolism 7 (<0.1%) participants.

The frequency and percentage of SAEs that occurred during the Booster Period that were designated as related by the Investigator are presented in the table below.

Table 51. Frequency and Percentage of Related SAEs After Third (Booster) Vaccination, Adult Main Study 301

System Organ Class Preferred Term	Original Monovalent N=13353 n (%)
Cardiac disorders	1 (0.0)
Acute myocardial infarction	1 (0.0)
Hepatobiliary disorders	1 (0.0)
Cholecystitis	1 (0.0)
Infections and infestations	1 (0.0)
Cellulitis	1 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.0)
Tendonitis	1 (0.0)
Respiratory, thoracic, and mediastinal disorders	2 (0.0)
Acute respiratory failure	1 (0.0)
Asthma	1 (0.0)
Pulmonary embolism	1 (0.0)
Vascular disorders	1 (0.0)
Deep vein thrombosis	1 (0.0)

Source: Reviewer table

Specific demographic information regarding the cases of SAEs that were designated as related by the Investigator are presented in the table below.

Table 52. Serious Adverse Events Considered Related by Investigator in the Booster Period, Safety Analysis Set, Adult Main Study 301

Investigational Product	Serious Adverse Event	Onset (Day After Vaccination)[a]	Age (Years)/Sex/Risk Factors	Resolution	Related (Per Applicant)
Original Monovalent Booster	Acute Myocardial Infarction	Day 3, 1st Booster	28/M History of IV heroin, marijuana use, current cigar/ vaping use, former tobacco user, alcohol use. Myocarditis and endocarditis were considered in the differential diagnosis; the final diagnosis was reported as non-ST elevation myocardial infarction. Investigator rationale for relatedness not provided, but there is a strong temporal relationship and biological plausibility.	Resolved	No
Original Monovalent Booster	Cholecystitis	Day 94, 1st Booster	37/M History of calculated BMI was 41.6 kg/m^2. Investigator rationale for relatedness was “early cases of cholelithiasis reported with this vaccine.” There is not a strong temporal relationship, and obesity was a risk factor.	Not resolved	No
Original Monovalent Booster	Hypersensitivity/ Cellulitis	Day 2, 1st Booster	59/M History of seasonal allergies, drug abuse, irregular heartbeat, and obesity (BMI was 41.8 kg/m^2). Hospitalized with worsening allergic reaction to study vaccine. An infectious diseases specialist felt that the event began as an allergic reaction that progressed to cellulitis. Treatment included intravenous (IV) antibiotic treatment with vancomycin and oral (PO) Benadryl. Both Investigator and Applicant reported this as a related event due to the temporal relationship.	Resolved	Yes

Investigational Product	Serious Adverse Event	Onset (Day After Vaccination)[a]	Age (Years)/Sex/Risk Factors	Resolution	Related (Per Applicant)
Original Monovalent Booster	Muscle edema, Tendonitis	Day 2, 1st Booster	51/F History not provided. The participant developed the participant experienced Type 1 fibrillary edema in the left biceps muscle and edema of the left biceps longus tendon and left supraspinatus tendon. The Investigator rationale for relatedness was the loss of force in the left arm after the first booster vaccination of study vaccine, which did not improve with physiotherapy. The Applicant thought there was insufficient information to establish causal association.	Not resolved	No
Original Monovalent Booster	Cerebrovascular Accident	Day 73, 1st Booster	57/M History of post-traumatic stress disorder. Magnetic resonance imaging showed an acute dissection of the right vertebral artery with acute/subacute ischemic infarcts of the right posterior medulla, vermis, and medial cerebellum. Investigator rationale for causality was that this was an inflammatory event that occurred two weeks post-injection event within the window period of reactogenicity. This rationale is problematic as the participant received the placebo at 2 weeks.	Resolved	No

Investigational Product	Serious Adverse Event	Onset (Day After Vaccination)[a]	Age (Years)/Sex/Risk Factors	Resolution	Related (Per Applicant)
Original Monovalent Booster	Acute Respiratory Failure, Asthma	Day 4, 2nd Initial Dose	49/F History of asthma since 1964, bronchitis, and pneumonia. Admitted to the hospital with a diagnosis of acute respiratory failure with hypoxia and asthma exacerbation. The Principal Investigator's rationale for relatedness was that the respiratory events were exacerbated upon administration of the booster vaccination based on medical records review of laboratory viral testing and medical examination findings documented by the Emergency Room (ER) Physician The medical history, cold weather at the time of presentation, and possibility of a viral trigger are alternative explanations. There is a temporal relationship that makes vaccine relatedness difficult to exclude.	Resolved	No
Original Monovalent Booster	Pulmonary Embolism, Thrombosis, Deep Vein Thrombosis	Day 6, 2nd Initial Dose	35/F History of nose surgery, seasonal allergies, oral contraceptive use, and headaches. The participant was diagnosed with deep vein thrombosis (DVT) and acute pulmonary embolism (PE). A venous ultrasound duplex of bilateral legs showed acute DVT of the left leg. Participant underwent venography, vein catheterization, and catheter-directed tPA. Participant underwent a second catheterization with tPA administration and stent placement for suspected May-Thurner syndrome (not proven). Per the Principal Investigator, the rationale for relatedness was that the event of deep vein thrombosis was potentially related to the concomitant medication Altavera. The Applicant cites Altavera use as a rationale for the deep vein thrombosis/ PE being unrelated to vaccine administration.	Resolved	No

Source: Reviewer table
Abbreviations: BMI=body mass index; DVT=deep vein thrombosis; ER=emergency room; F=female; IV=intravenous; M=male; PE=pulmonary embolism; PO=*per os*; tPA=tissue plasminogen activator

Clinical Reviewer Comment: Of the SAEs that were designated as related by the Investigator, the ones that were the most clinically relevant were the participant with acute myocardial infarction 3 days after vaccine administration, the participant with hypersensitivity/cellulitis 2 days after vaccine administration, and the participant with tendonitis and muscle edema 2 days after vaccination. In these cases, vaccine relatedness cannot be entirely excluded due to the strong temporal relationship between these events and vaccine administration. The other SAEs that occurred during the Booster Period that were deemed related by the Investigator had confounding variables that make vaccine relatedness less certain. The Investigator/ Applicant assessment that the remaining SAEs that occurred during the Booster Vaccination Period are reasonable.

Clinical Reviewer Summary Comment—SAEs: In summary, there were low numbers for the percentages of participants who experienced an SAE with no imbalances noted in the placebo-controlled portion of the trial. The overall percentages of participants with SAEs in the Blinded Crossover and Booster Vaccination Periods were comparable to the Initial Vaccination Period. In addition, 6 cardioembolic events were reported with close temporal association to vaccination, and even though most of these participants had risk factors, a relationship between these events and Original Monovalent cannot be definitively excluded.

6.1.12.5 Adverse Events of Special Interest (AESI)

Unsolicited Adverse Events of Clinical Interest

Adverse Events of Special Interest

AESIs for Adult Main Study 301 included PIMMCs (potential immune-mediated medical conditions) and AEs representing complications specific to COVID-19. The AEs representing complications specific to COVID-19 were reviewed, and no concerns for vaccine-enhanced disease were identified.

A summary of the frequency and percentage of PIMMCs based on Investigator reporting and protocol-defined criteria for ≥1 participant in the Original Monovalent group during the Initial Vaccination Period for the Safety Analysis Set is presented in the table below.

Table 53. Frequency and Percentage of Potential Immune-Mediated Medical Conditions Based on Investigator Reporting and Protocol-Defined Criteria for ≥1 Participant in the Original Monovalent Group During the Initial Vaccination Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Any System Organ Class	39 (0.2)	21 (0.2)
Nervous system disorders	11 (<0.1)	8 (<0.1)
Neuropathy peripheral	3 (<0.1)	3 (<0.1)
Seizure	3 (<0.1)	2 (<0.1)
Bell's palsy	2 (<0.1)	1 (<0.1)
Nervous system disorder	1 (<0.1)	0
Neuralgia	1 (<0.1)	0
Partial seizures	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	7 (<0.1)	5 (<0.1)
Rheumatoid arthritis	3 (<0.1)	2 (<0.1)
Ankylosing spondylitis	1 (<0.1)	0
Arthritis	1 (<0.1)	0
Bursitis	1 (<0.1)	0
Polymyalgia rheumatica	1 (<0.1)	1 (<0.1)

System Organ Class/ Preferred Term	Original Monovalent N=19735 n (%)	Placebo N=9847 n (%)
Skin and subcutaneous tissue disorders	5 (<0.1)	3 (<0.1)
Psoriasis	2 (<0.1)	2 (<0.1)
Alopecia	1 (<0.1)	0
Alopecia areata	1 (<0.1)	0
Erythema nodosum	1 (<0.1)	0
Cardiac disorders	3 (<0.1)	1 (<0.1)
Ischemic cardiomyopathy	1 (<0.1)	0
Left ventricular dilation	1 (<0.1)	0
Myocarditis	1 (<0.1)	0
Endocrine disorders	3 (<0.1)	1 (<0.1)
Basedow's disease	2 (<0.1)	0
Autoimmune thyroiditis	1 (<0.1)	1 (<0.1)
Eye disorders	3 (<0.1)	2 (<0.1)
Uveitis	2 (<0.1)	1 (<0.1)
Iridocyclitis	1 (<0.1)	0
Blood and lymphatic system disorders	2 (<0.1)	1 (<0.1)
Thrombocytopenia	2 (<0.1)	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	0
Crohn’s disease	1 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	0
Autoimmune hepatitis	1 (<0.1)	0
Injury, poisoning and procedural complications	1 (<0.1)	0
Chilblains	1 (<0.1)	0
Investigations	1 (<0.1)	0
Heparin-induced thrombocytopenia test positive	1 (<0.1)	0
Vascular disorders	1 (<0.1)	0
Deep vein thrombosis	1 (<0.1)	0

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report, Table 198, Pages 420-421
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; Original Monovalent=5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant; PIMMC=potential immune-mediate medical condition.

The overall percentages of participants who had PIMMCs was balanced between the vaccine and placebo arms during the Initial Vaccination Period (0.2% versus 0.2%). No PIMMC event occurred in more than 0.1% of participants in either the vaccine or placebo group.

The narrative information for PIMMC’s was reviewed for the Initial Vaccination Period, and 14 participants had related PIMMCs per the Investigator, 2 participants with Rheumatoid Arthritis, 1 participant with Basedow’s Disease, 1 participant with Chilblains, 1 participant with Thrombocytopenia, 2 participants with Neuropathy Peripheral, 1 participant with Arthritis, 1 participant with Alopecia, 1 participant with Bursitis, 1 participant with Nervous System Disorder, 1 participant with Neuralgia, 1 participant with Alopecia Areata, and 1 participant with 2 Uveitis events. The narrative information for these cases is summarized as follows:

- Rheumatoid Arthritis, considered related by the Principal Investigator (temporal relationship, occurred 21 days after 1st vaccination, no other rationale provided). However, this participant had a medical history of immune-mediated chronic illness (immune thrombocytopenic purpura, lichen sclerosis, morphea, and rosacea), and the clinical picture for Rheumatoid Arthritis was not clear (no X-ray findings and a clinical picture was not entirely consistent with Rheumatoid Arthritis)

- Basedow's Disease, considered related by the Principal Investigator (temporal relationship, 28 days after 2nd vaccination, rationale was that “study vaccine administration” may have triggered Basedow’s/ Grave’s Disease). However, the participant had abnormal thyroid laboratory studies that predate vaccination suggesting the Basedow’s Disease was pre-existing and undiagnosed.
- Chilblains, considered related by the Principal Investigator (temporal relationship, 40 days after 2nd vaccination, rationale was that this event was “immune mediated”). However, this participant had a history of autoimmune conditions.
- Thrombocytopenia, considered related by the Principal Investigator (temporal relationship, 31 days after 2nd vaccination). Discussed as an SAE, temporal association with Losartan (can cause thrombocytopenia) makes vaccine relatedness unlikely.
- Neuropathy peripheral, Nervous system disorder (temporal relationship, same day as initial vaccination). Condition did not change with additional doses of the blinded study vaccine.
- Arthritis, considered related by the Principal Investigator and Applicant (temporal relationship, 8 days after initial vaccination). Per the Investigator, “likely a musculoskeletal or connective tissue disorder.”
- Alopecia, considered related by the Principal Investigator (50 days after initial vaccination, no investigator rationale). The participant had a prior history of hair loss which confounds vaccine relatedness.
- Bursitis, considered related by the Principal Investigator (temporal relationship, 13 days after initial vaccination, no Investigator rationale). The participant had history of joint disease and her inflammatory markers were mostly negative (weakly positive ANA with speckled pattern) which confounds vaccine relatedness.
- Nervous system disorder, considered related by the Principal Investigator and Applicant (temporal relationship, 1 day after initial vaccination, no investigator rationale). No unifying diagnosis was made, and this case is confounded by the fact that the participant was physically assaulted two days prior to symptom onset and prior to the second vaccination.
- Neuralgia, considered related by the Principal Investigator and Applicant (temporal relationship, 21 days after initial vaccination). The rationale for relatedness was, “exacerbation of chronic neuropathy and evidence of new polyneuropathy in the setting of likely second initial vaccination represented a potential immune-mediated medical condition, hence assessed as an immune-mediated peripheral neuropathy.”
- Alopecia areata, considered related by the Principal Investigator and Applicant (temporal relationship, 40 days after receiving the second vaccination). The participant experienced a stress event which could have confounded the possibility of vaccine relatedness.
- Rheumatoid arthritis, considered related by the Principal Investigator and Applicant (temporal relationship, 2 days after receiving the second vaccination). There was a strong temporal association between the onset of symptoms (bilateral hand numbness and swelling with no known triggers) and vaccine administration.
- Neuropathy peripheral, considered related by the Principal Investigator and Applicant (temporal relationship, 25 days after receiving the first vaccination). Rationale for relatedness was not provided, but the narrative thought that temporal relationship was

"less plausible", arguing against relatedness.

- Uveitis, two events, considered related by the Principal Investigator and Applicant (temporal relationship, 7 days after receiving the first initial vaccination). Rationale for relatedness was the temporal sequence and recurrence following the second initial vaccination.

Reviewer Comment: For most of the narrative cases presented, vaccine relatedness could not be excluded due to biologic plausibility, and temporal relationship, or both. In some cases, relatedness was agreed upon by both the Investigator and the Applicant. Notable cases where vaccine relatedness is less likely despite Investigator assessment included Basedow's Disease, Chilblains, and Thrombocytopenia.

The other cases in Table 53 above were deemed unrelated by the Investigator and Applicant. In some cases, there was a temporal association between the event and vaccine administration; however, considering these events unrelated to vaccine administration was not unreasonable due to questionable biologic plausibility. It is reasonable, however, to conclude that there is a possibility of developing PIMMCs after administration of the Original Monovalent vaccine during the Initial Vaccination Period. This conclusion was also acknowledged as part of the original EUA reviews and Facts Sheets.

There was no narrative provided for the participant who developed myocarditis as a PIMMC.

A summary of the frequency and percentage of PIMMCs based on investigator reporting and protocol-defined criteria for ≥1 participant in the Original Monovalent group during the Blinded Crossover Period for the Safety Analysis Set is presented in the table below.

Table 54. Frequency and Percentage of Potential Immune-Mediated Medical Conditions Based on Investigator Reporting and Protocol Defined Criteria for ≥1 Participant in the Placebo to Original Monovalent Group During the Blinded Crossover Vaccination Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Any System Organ Class	16 (0.2)	32 (0.2)
Nervous system disorders	5 (<0.1)	9 (<0.1)
Seizure	3 (<0.1)	4 (<0.1)
Bell's palsy	1 (<0.1)	1 (<0.1)
Neuralgic amyotrophy	1 (<0.1)	0
Vitiligo	1 (<0.1)	2 (<0.1)
Alopecia areata	1 (<0.1)	0
Granulomatous dermatitis	1 (<0.1)	0
Pruritus	1 (<0.1)	0
Urticaria	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	3 (<0.1)	10 (<0.1)
Rheumatoid arthritis	1 (<0.1)	3 (<0.1)
Arthralgia	1 (<0.1)	0
Myalgia	1 (<0.1)	0
Pain in extremity	1 (<0.1)	0
Scleroderma	1 (<0.1)	0

System Organ Class/ Preferred Term	Placebo to Original Monovalent N=6416 n (%)	Original Monovalent to Placebo N=15298 n (%)
Cardiac disorders	2 (<0.1)	2 (<0.1)
Left atrial dilatation	1 (<0.1)	0
Myocarditis	1 (<0.1)	0
Pericarditis	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	0
Colitis microscopic	1 (<0.1)	0
General disorders and administration site conditions	1 (<0.1)	1 (<0.1)
Systemic inflammatory response syndrome	1 (<0.1)	0
Immune system disorders	1 (<0.1)	0
Sarcoidosis	1 (<0.1)	0

Source: 2019nCoV-301: Adult 17 Month Clinical Study Report, Table 198, Pages 421-422
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm; PIMMC=potential immune-mediate medical condition.

No PIMMC event occurred in more than 0.1% of participants in either treatment group. Regarding PIMMCs, the safety profile of the Original Monovalent vaccine during the Blinded Crossover Period was comparable to the Initial Vaccination Period.

The narrative information for PIMMC's was reviewed for the Blinded Crossover Period, and 10 participants had related PIMMCs per the Investigator, 6 in the Placebo to Original Monovalent group and 4 in the Original Monovalent to Placebo Group. The narrative information for these cases is summarized as follows:

Placebo to Original Monovalent:

- Scleroderma, considered related by the Principal Investigator (no temporal relationship, 128 days after receiving the 2nd crossover Original Monovalent vaccine, No clear investigator rationale). The lack of a clear temporal relationship and risk factors for collagen overproduction (female sex, Native American ethnicity, and history of pre-diabetes and obesity) confound the ability to attribute the Scleroderma to vaccine administration.
- Pericarditis and Myocarditis, considered related by the Principal Investigator (temporal relationship, 10 days after receiving the 1st crossover Original Monovalent vaccine). Per the Investigator, the probability of either myocarditis or pericarditis as the etiology is comparable, and myocarditis was not completely ruled out. The Applicant cited a sick contact and elevated ASO titers as a possible alternative etiology and stated that this diagnosis was not confirmed by Cardiology.
- Myalgia, Arthralgia, and Pain in Extremity, considered related by the Principal Investigator and Applicant (temporal relationship, 10 days after receiving the 1st crossover Original Monovalent vaccine). The narrative also states that there is not enough available diagnostic information to assess causality of these events.
- Vitiligo, considered related by the Principal Investigator (temporal relationship, 25 days after receiving the 2nd crossover Original Monovalent vaccine). Per the Principal Investigator, "time coincidence of the event", autoimmune nature of vitiligo, and several similar cases of vitiligo being diagnosed within weeks of COVID-19 vaccination were cited as the rationale for relatedness. Confounders in this case include concomitant administration of the Pfizer COVID-19 vaccine and a family history of autoimmune

disease.

- Urticaria and Pruritus, considered related by the Principal Investigator (temporal relationship, 1 days after receiving the 2nd crossover Original Monovalent vaccine). Investigator rationale for relatedness is not provided. The argument that vaccine administration was not related to the urticaria and pruritus included the participant's history of childhood asthma and environmental allergies.
- Neuralgic Amyotrophy, considered related by the Principal Investigator and the Applicant (temporal relationship, 3 days after receiving the 1st crossover Original Monovalent vaccine). This case is confounded by Parsonage Turner Syndrome.

Original Monovalent to Placebo:

- Psoriasis, considered related by the Principal Investigator and the Applicant (no temporal relationship, 7 months days after receiving the second initial Original Monovalent vaccination). "The event is attributed to pre-existing long standing history of (three years) dermatological conditions like seborrheic keratosis, with a clinical presentation characterized by waxing and waning periods." No other confounding issues were presented in the narrative.
- Optic Neuritis, considered related by the Principal Investigator and the Applicant (temporal relationship, 104 days after receiving the second initial Original Monovalent vaccination). The Investigator attributed related to symptom onset 14 days after receiving the blinded study vaccine, which in this case was the placebo. There was no temporal association between symptom onset and the last dose of vaccine received. Per the Applicant, "The plausible etiology was assessed as non-traumatic, including possible transient ischemic attack/stroke, ischemic origin, giant cell arteritis, or sarcoidosis."
- Systemic Lupus Erythematosus, Psoriatic Arthropathy, (no temporal relationship, 32 weeks after receiving the second initial Original Monovalent vaccination). The investigator rationale in this narrative is difficult to understand, likely due to a typo, and per the Applicant, this participant had a history of Systemic Lupus Erythematosus and Psoriatic Arthropathy. Given the medical history and lack of temporal association, vaccine relatedness is unlikely.

Reviewer Comment: Of the narratives of events deemed related by the Investigator, most had a strong temporal relationship to vaccine administration with confounding information which made vaccine relatedness less likely. Of these cases, the most clinically relevant event, which despite potentially confounding information, was likely to be related to vaccine administration was the myocarditis/ pericarditis case. Though not felt to be attributable to vaccine, the narratives for Bell's palsy were reviewed, and only one case had a narrative. It is presented below.

- A 43-year-old White Hispanic or Latino male participant in the Placebo to Original Monovalent Group developed Bell's palsy 19 days after receiving the 1st Original Monovalent crossover vaccination. This case was considered unrelated, but no alternative etiology was provided and there was a strong temporal relationship. Vaccine relatedness cannot be excluded.

A summary of the frequency and percentage of PIMMCs based on Investigator reporting and protocol-defined criteria for ≥1 participant in the Original Monovalent group during the Booster Vaccination Period for the Safety Analysis Set is presented in the table below.

Table 55. Frequency and Percentage of Potential Immune-Mediated Medical Conditions Based on Investigator Reporting and Protocol Defined Criteria During the Booster Vaccination Period, Booster Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent Booster N=13353 n (%)
Any System Organ Class	27 (0.2)
Nervous system disorders	7 (<0.1)
Neuropathy peripheral	2 (<0.1)
Bell's palsy	2 (<0.1)
Facial paralysis	1 (<0.1)
Guillain-Barre syndrome	1 (<0.1)
Seizure	1 (<0.1)
Musculoskeletal and connective tissue disorders	5 (<0.1)
Arthralgia	1 (<0.1)
Polyarthritis	1 (<0.1)
Psoriatic arthropathy	1 (<0.1)
Rheumatoid arthritis	1 (<0.1)
Sjogren's syndrome	1 (<0.1)
Skin and subcutaneous tissue disorders	7 (<0.1)
Psoriasis	3 (<0.1)
Alopecia areata	2 (<0.1)
Cutaneous vasculitis	1 (<0.1)
Lichen planus	1 (<0.1)
Blood and lymphatic system disorders	2 (<0.1)
Immune thrombocytopenia	1 (<0.1)
Thrombocytopenia	1 (<0.1)
Ear and labyrinth disorders	1 (<0.1)
Deafness neurosensory	1 (<0.1)
Endocrine disorders	0
Basedow's disease	0
Eye disorders	1 (<0.1)
Uveitis	1 (<0.1)
General disorders and administration site conditions	1 (<0.1)
Chest pain	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)
Autoimmune hepatitis	1 (<0.1)
Immune system disorders	1 (<0.1)
Anaphylactic reaction	1 (<0.1)
Infections and infestations	1 (<0.1)
Endophthalmitis	1 (<0.1)
Metabolism and nutrition disorders	0
Type 1 diabetes mellitus	0
Respiratory, thoracic, and mediastinal disorders[a]	1 (<0.1)
Pulmonary fibrosis[a]	1 (<0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)[a]	1 (<0.1)
Chronic lymphocytic leukemia[a]	1 (<0.1)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Table 112, Page 228-229
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); n=unique number of participants experiencing the adverse event; N=number of participants in the Booster Safety Analysis Set; PIMMC=potential immune-mediate medical condition
a. Events of Respiratory, Thoracic, and Mediastinal Disorder/Pulmonary fibrosis and Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)/chronic lymphocytic leukemia were erroneously not included in the original CSR.

No PIMMC event occurred in more than 0.1% of participants during the Booster Vaccination Period. For PIMMCs, the safety profile of the Original Monovalent vaccine during the Booster Vaccination Period was comparable to the Initial Vaccination and Blinded Crossover Periods.

No PIMMCs were considered to be related to booster vaccine administration by the Principal Investigator or the Applicant. Of the available narratives, excluding vaccine relatedness was not unreasonable. There were 4 narratives that are being included for further consideration because they relate to the current proposed labeling:

- A 53-year-old male participant from Mexico experienced facial paralysis 7 days after Original Monovalent booster vaccination. The participant had a history of idiopathic facial paralysis which confounded attributing his symptoms to vaccine administration. Given the strong temporal association, however, vaccine relatedness cannot be entirely excluded.
- A 45-year-old White, Hispanic, or Latino male participant developed Guillain-Barré syndrome (GBS) 90 days after Original Monovalent booster vaccination. The Applicant did not consider this event related because there was not a strong temporal relationship, and the participant had a recent GI illness which was cited as a risk factor for developing GBS.
- A 40-year-old Black or African American male participant developed Bell's palsy 36 days after Original Monovalent booster vaccination. The narrative did not provide sufficient information to exclude other etiologies. Because there is still a temporal relationship, vaccine relatedness cannot be entirely excluded.
- A 41-year-old White male participant developed Bell's palsy 94 days after Original Monovalent booster vaccination. The lack of a temporal relationship makes vaccine relatedness unlikely.

In summary, there were overall few events of PIMMCs, no imbalances noted in the placebo-controlled period, with generally comparable types of events and time to onset. In the absence of a longer term, placebo-controlled safety data collection period, it is difficult to discern background rates of relatively common medical conditions (e.g., rheumatoid arthritis) from potentially immune-mediated events related to vaccination with a long latency. In addition, some PIMMCs were reported in closer temporal association to vaccination and with no clear alternative etiology identified (including Bell's palsy and peripheral neuropathy), and for these events a relationship to Original Monovalent cannot be definitively excluded, although no imbalances were noted overall.

> *Reviewer Comment: Cranial nerve AESIs were reported on Study 311. Though the above cases were insufficient to establish a safety signal, in context of the Study 311 data, the clinical review team determined that cranial nerve AESIs including Bell's palsy should remain in labeling. For further discussion, please see Section* 6.4.12.

Adverse Events of Special Interest

Myocarditis/Pericarditis

Of particular interest were events of myocarditis and pericarditis. Postmarketing data from individuals receiving mRNA vaccines have demonstrated increased risks of myocarditis and pericarditis, particularly within 7 days following the second primary series dose. The observed risk has been highest in adolescent and young adult males. There were 4 myocarditis/

pericarditis events (2 myocarditis and 1 pericarditis in the vaccine group and 1 case of pericarditis in the placebo group) that occurred in Adult Main Study 301.

Anaphylaxis

One (<0.1%) participant experienced an SAE of anaphylactic reaction 19 days after receiving the booster vaccination, this event was assessed by the investigator and Applicant as not related to trial vaccine. Per the narrative, the event was attributed by the treating physician as a food allergy. Vaccine relatedness is unlikely. Anaphylaxis is already addressed in labeling.

Relevant SMQs

The SMQs that were provided that analyzed the pre-crossover period were analyzed to further address AESIs. In general,

All Cardiac Events

The SMQ for Ischemic Heart Disease for the Pre-Crossover Period for Adult Main Study 301 is presented in the table below.

Table 56. Number of Events and the Events Rates for Ischemic Heart Disease (SMQ) Reported in Pre-Crossover Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent[a] N=19735	Placebo[a] N=9847
Total follow-up time post-Dose 1, person-years	6897.6	3641.1
Mean follow-up time post-Dose 1, days	127.7	135.1
Median follow-up time post-Dose 1, days	97	96
Any SMQs (Events), n (rate per 100 person-years), (95% CI)	18 (0.26), (0.15, 0.41)	8 (0.22), (0.09, 0.43)
Number of participants with SMQ, n (%)[b]	17 (0.09)	7 (0.07)
Received Dose 1, n (%)	17 (100.00)	7 (100.00)
Mean follow-up time (days)	200.4	162.1
Received Dose 2, n (%)	16 (94.12)	6 (85.71)
Mean follow-up time (days)	205.8	97.2
Cardiac disorders, n (rate per 100 person-years), (95% CI)	18 (0.26), (0.15, 0.41)	8 (0.22), (0.09, 0.43)
Acute coronary syndrome, n (%)	1 (0.01)	0 (0.00)
Acute myocardial infarction, n (%)	3 (0.04)	4 (0.11)
Angina pectoris, n (%)	2 (0.03)	0 (0.00)
Coronary artery disease, n (%)	3 (0.04)	1 (0.03)
Coronary artery occlusion, n (%)	1 (0.01)	0 (0.00)
Ischemic cardiomyopathy, n (%)	1 (0.01)	0 (0.00)
Myocardial infarction, n (%)	6 (0.09)	3 (0.08)
Stress cardiomyopathy, n (%)	1 (0.01)	0 (0.00)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR page 4116
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PY=person-years; SOC=system organ class; SMQ=standard MedDRA Query
a. Treatment group applicable to period.
b. Percent calculated based on number of participants in safety analysis set in each treatment period.
Note: At the SOC level, the number of events, event rate per 100 PY, and 95% CI for event rate are presented in first row, with the following rows based on participants experiencing events within the SOC. The 95% CI is calculated using the Poisson distribution.
Based on data extract: 2022-11-23. MedDRA 25.0.
SOCs are sorted by descending order of frequency, PTs are sorted by alphabetic order.

The event rate per 100 person-years for ischemic heart disease in the vaccine group was 0.26 (95% CI: 0.15, 0.41) versus 0.22 (95% CI: 0.09, 0.43) in the placebo group.

The SMQ for Cardiac Failure for the Pre-Crossover Period of Adult Main Study 301 is presented in the table below.

Table 57. Number of Events and the Events Rates for Cardiac Failure (SMQ) Reported in Pre-Crossover Period, Safety Analysis Set, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent[a] N=19735	Placebo[a] N=9847
Total follow-up time post-Dose 1, person-years	6897.6	3641.1
Mean follow-up time post-Dose 1, days	127.7	135.1
Median follow-up time post-Dose 1, days	97	96
Any SMQs (Events), n (rate per 100 person-years), (95% CI)	34 (0.49), (0.34, 0.69)	9 (0.25), (0.11, 0.47)
Number of participants with SMQ, n (%)[b]	30 (0.15)	8 (0.08)
Received Dose 1, n (%)	30 (100.00)	8 (100.00)
Mean follow-up time, days	146.4	122.6
Received Dose 2, n (%)	28 (93.33)	8 (100.00)
Average follow-up time, days	136.0	122.6
General disorders and administration site conditions n (rate per 100 person-years), (95% CI)	17 (0.25), (0.14, 0.39)	4 (0.11), (0.03, 0.28)
Edema, n (%)	1 (0.01)	0 (0.00)
Edema peripheral, n (%)	12 (0.17)	3 (0.08)
Peripheral swelling, n (%)	4 (0.06)	1 (0.03)
Cardiac disorders, n (rate per 100 person-years), (95% CI)	11 (0.16), (0.08, 0.29)	2 (0.05), (0.01, 0.20)
Acute left ventricular failure, n (%)	1 (0.01)	0 (0.00)
Cardiac failure acute, n (%)	1 (0.01)	0 (0.00)
Cardiac failure congestive, n (%)	5 (0.07)	2 (0.05)
Chronic left ventricular failure, n (%)	2 (0.03)	0 (0.00)
Cor pulmonale acute, n (%)	1 (0.01)	0 (0.00)
Left ventricular dilatation, n (%)	1 (0.01)	0 (0.00)
Respiratory, thoracic, and mediastinal disorders, n (rate per 100 person-years), (95% CI)	6 (0.09), (0.03, 0.19)	3 (0.08), (0.02, 0.24)
Acute pulmonary edema, n (%)	1 (0.01)	0 (0.00)
Pulmonary congestion, n (%)	5 (0.07)	3 (0.08)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR page 4120
a. Treatment group applicable to period.
b. Percent calculated based on number of participants in safety analysis set in each treatment period.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PY=person-years; SOC=system organ class; SMQ=standard MedDRA Query
Note: At the SOC level, the number of events, event rate per 100 PY, and 95% CI for event rate are presented in first row, with the following rows based on participants experiencing events within the SOC. The 95% CI is calculated using the Poisson distribution.
Based on data extract: 2022-11-23. MedDRA 25.0.
SOCs are sorted by descending order of frequency, PTs are sorted alphabetically.

The event rate per 100 person-years for congestive heart failure in the vaccine group was 0.49 (95% CI: 0.34, 0.69) versus 0.25 (95% CI: 0.11, 0.47) in the placebo group.

Reviewer Comment: The event rate per 100 person-years for Any Cardiac Failure SMQ was twice as high in the vaccine group as in the placebo group (0.49 (95% CI: 0.34, 0.69) versus 0.25 (95% CI: 0.11, 0.47)). Numeric imbalances were observed in the individual preferred terms. Cardiac Failure was removed from the current proposed labeling, but because numerical imbalances were noted the clinical team will recommend that heart failure continue to be included in labeling.

The SMQ for Cardiac Arrhythmias for the Pre-Crossover Period of Adult Main Study 301 is presented in the table below.

Table 58. Number of Events and the Events Rates for Cardiac Arrhythmias (SMQ) Reported in Pre-crossover Period, Safety Analysis Set, Adult Main Study 301

System Organ Class Preferred Term	Original Monovalent[a] N=19735	Placebo[a] N=9847
Total follow-up time post-Dose 1, person-years	6897.6	3641.1
Mean follow-up time post-Dose 1, days	127.7	135.1
Median follow-up time post-Dose 1, days	97	96
Any SMQs (Events), n (rate per 100 person-years), (95% CI)	69 (1.00), (0.78, 1.27)	28 (0.77), (0.51, 1.11)
Number of participants with SMQ, n (%)[b]	63 (0.32)	27 (0.27)
Received Dose 1, n (%)	63 (100.00)	27 (100.00)
Average follow-up time, days	167.3	160.5
Received Dose 2, n (%)	55 (87.30)	22 (81.48)
Average follow-up time, days	176.5	170.0
Cardiac disorders, n (rate per 100 person-years), (95% CI)	51 (0.74), (0.55, 0.97)	18 (0.49), (0.29, 0.78
Arrhythmia, n (%)	1 (0.01)	0 (0.00)
Atrial fibrillation, n (%)	13 (0.19)	4 (0.11)
Atrial flutter, n (%)	1 (0.01)	0 (0.00)
Atrioventricular block complete, n (%)	1 (0.01)	0 (0.00)
Atrioventricular block first degree, n (%)	1 (0.01)	1 (0.03)
Bradycardia, n (%)	4 (0.06)	1 (0.03)
Cardiac arrest, n (%)	5 (0.07)	4 (0.11)
Cardio-respiratory arrest, n (%)	0 (0.00)	1 (0.03)
Extrasystoles, n (%)	1 (0.01)	0 (0.00)
Palpitations, n (%)	4 (0.06)	1 (0.03)
Sinus arrest, n (%)	0 (0.00)	1 (0.03)
Sinus tachycardia, n (%)	3 (0.04)	0 (0.00)
Supraventricular extrasystoles, n (%)	1 (0.01)	0 (0.00)
Supraventricular tachycardia, n (%)	2 (0.03)	0 (0.00)
Tachycardia, n (%)	10 (0.14)	5 (0.14)
Ventricular extrasystoles, n (%)	2 (0.03)	0 (0.00)
Ventricular tachycardia, n (%)	2 (0.03)	0 (0.00)
Nervous system disorders, n (rate per 100 person-years), (95% CI)	13 (0.19), (0.10, 0.32)	10 (0.27), (0.13, 0.51)
Syncope, n (%)	13 (0.19)	10 (0.27)
Investigations, n (rate per 100 person-years), (95% CI)	5 (0.07), (0.02, 0.17)	0 (0.00), (NA, 0.10)
Heart rate increased, n (%)	5 (0.07)	0 (0.00)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR page 4126
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; PY=person-years; SOC=system organ class; SMQ=standard MedDRA Query
a. Treatment group applicable to period.
b. Percent calculated based on number of participants in safety analysis set in each treatment period.
Note: At the SOC level, the number of events, event rate per 100 PY, and 95% CI for event rate are presented in first row, with the following rows based on participants experiencing events within the SOC. The 95% CI is calculated using the Poisson distribution.
Based on data extract: 2022-11-23. MEDDRA 25.0.
SOCs are sorted by descending order of frequency, PTs are sorted by alphabetic order.

Reviewer Comment: The SMQs for ischemic heart disease and cardiac arrhythmia demonstrated reasonably balanced event rates for the vaccine compared with the placebo group; however, the event rates in Any Cardiac Failure SMQ (including terms related to congestive heart failure) were twice as high in the vaccine group compared with the placebo

group [0.49 (95% CI: 0.34, 0.69) versus 0.25 (95% CI: 0.11, 0.47), respectively.] *Of note, confidence intervals are overlapping. A numerical imbalance in cardiac failure was also acknowledged during the EUA review of the Original Monovalent Vaccine primary series and will be added to Section 6.1 of the current USPI.*

A numeric imbalance in Atrial fibrillation/ Atrial flutter was noted in this SMQ. Please see the discussion of Atrial Fibrillation under SAEs for further analysis of this potential safety signal.

Hypersensitivity Reactions

The SMQ (narrow and broad) for hypersensitivity for the Pre-Crossover Period of Adult Main Study 301 is presented in the table below.

Table 59. Frequency and Percentage of Hypersensitivity Events, Adult Main Study 301

Preferred Term	Original Monovalent N=19735	Placebo N=9847
Any SMQs (events) n (e/100 PY), (95% CI)	260 (3.77), (3.33, 4.26)	89 (2.44), (1.96, 3.01)
Number of participants with SMQ, n (%)	237 (1.20)	84 (0.85)
Rash	48 (0.70)	22 (0.60)
Pruritus	24 (0.35)	2 (0.05)
Urticaria	18 (0.26)	6 (0.16)
Dermatitis contact	15 (0.22)	3 (0.08)
Conjunctivitis	9 (0.13)	2 (0.05)
Wheezing	7 (0.10)	3 (0.08)
Dermatitis atopic	6 (0.09)	1 (0.03)
Drug hypersensitivity	6 (0.09)	1 (0.03)
Erythema	7 (0.10)	2 (0.05)
Sneezing	5 (0.07)	2 (0.05)
Swelling of eyelid	5 (0.07)	0
Flushing	5 (0.07)	2 (0.05)
Acute respiratory failure	4 (0.06)	0
Stomatitis	4 (0.06)	1 (0.03)
Rash maculopapular	3 (0.04)	0
Eye swelling	3 (0.04)	0
Swelling face	3 (0.04)	0
Injection site rash	3 (0.04)	0
Angioedema	2 (0.03)	0
Lip swelling	2 (0.03)	0

Source: Integrated Summary of Safety, Table 50, Page 128-131
Abbreviations: CI=confidence interval; PY=person years; SMQ=Standard Medical Dictionary for Regulated Activities Query; e/100 PY=event rate per 100 person years.

The event rate per 100 person-years for hypersensitivity in the vaccine group was 3.77 (95% CI 3.77, 4.26) versus 2.44 (95% CI 1.96, 3.01) in the placebo group. There is an imbalance between the vaccine and placebo group event rates, but hypersensitivity reactions have already been addressed in labeling. This safety information was analyzed and does not contain any imbalances that require further adjustments to the labeling.

One serious case of angioedema initially began as generalized urticaria in a 32-year-old woman 2 days after Dose 1 of Original Monovalent. The reaction progressed to angioedema of the lips and tingling of the tongue, for which she sought medical attention and was treated with epinephrine, corticosteroids, and antihistamines. This participant was evaluated as an outpatient by an allergist-immunologist, who did not consider the reaction to represent an IgE-mediated process (i.e., anaphylaxis) or a severe cutaneous drug reaction, but rather acute urticaria and

dermatographism resulting from a combination of potential triggers, including an adjuvanted vaccine, nitrofurantoin (for an intercurrent urinary tract infection), perimenstrual hormone shifts, and ibuprofen.

Hypertension

The Applicant did not provide an updated SMQ of hypertension in their Clinical Study Reports. There were 6 participants in the initial vaccination period with a Preferred Term corresponding to hypertension, 5 in the vaccine group, and 1 in the placebo group [Preferred Terms were Hypertension (vaccine n=2), Hypertensive Crisis (vaccine n=1, placebo n=1), Hypertensive Emergency (vaccine n=1), and Hypertensive Urgency (vaccine n=1)]. The time to onset for serious events in the Original Monovalent arm ranged from 11 to 90 days following the most recent dose of Original Monovalent. In all cases, the participants had a history of hypertension. Though there was a numerical imbalance, none of the cases in the vaccine group had convincing information to suggest vaccine relatedness. There is no clear indication of a safety signal for hypertension.

Biliary Events

The SMQ (narrow and broad) for biliary disorders for the Pre-Crossover Period of Adult Main Study 301 is summarized in the table below.

Table 60. Biliary Disorders, Adult Main Study 301

Parameter	Original Monovalent N=19735	Placebo N=9847
Any SMQs, (events), n (e/100 PY), (95% CI)	20 (0.29), (0.18,0.45)	4 (0.11), (0.03, 0.28)
Number of participants with SMQ, n (%)	16 (0.08)	3 (0.03)

Source: Integrated Summary of Safety, Table 50, Page 128-131

Abbreviations: CI=confidence interval; e/100 PY=incidence rate per 100 person years; n=number of events or number of participants exhibiting the event; SMQ=Standard Medical Dictionary for Regulated Activities Query; N=number of participants with SMQ

The event rate per 100 person-years for biliary disorders in the vaccine group was 0.20 (95% CI: 0.18, 0.45) versus 0.11 (95% CI: 0.03, 0.28) in the placebo group. This imbalance was already noted during the EUA review of the Original Monovalent Vaccine primary series, and acute cholecystitis was included in the EUA Fact Sheet under Section 6. Acute cholecystitis will also be placed in Section 6.1 in the USPI as there continues to be an imbalance the biliary disorder safety data, and Novavax has not provided sufficient scientific justification to remove acute cholecystitis from the USPI.

Neurovascular Events

The SMQ (narrow and broad) for neurovascular events for the Pre-Crossover Period of Adult Main Study 301 is summarized in the table below.

Table 61. Central Nervous System Vascular Disorders, Adult Main Study 301

Parameter	Original Monovalent N=19735	Placebo N=9847
Any SMQs (events), n (e/100 PY), (95% CI)	14 (0.20), (0.11, 0.34)	6 (0.16), (0.06, 0.36)
Number of participants with SMQ, n (%)	14 (0.07)	6 (0.06)

Source: Integrated Summary of Safety, Table 50, Page 128-131

Abbreviations: CI=confidence interval; e/100 PY=incidence rate per 100 person years; n=number of events or number of participants exhibiting the event; N=number of participants with SMQ; SMQ=Standard Medical Dictionary for Regulated Activities Query

This analysis shows a small rate imbalance; however, it becomes more clinically suspicious in the setting of the imbalance in atrial fibrillation. The event rate per 100 person-years for vascular disorders in the vaccine group was 0.20 (95% CI: 0.11, 0.34) versus 0.16 (95% CI: 0.06, 0.36) in the placebo group

Evaluation of the SAE narrative information reveled:

Guillain-Barre Syndrome/Neuropathy

One participant in Adult Main Study 301 reported an event consistent with Guillain-Barré syndrome (GBS) during the booster period 90 days after the first booster vaccination. In general, GBS is already addressed in the USPI, and this case was not as clinically concerning (i.e., occurred 90 days after vaccination and in the context of a GI infection). This case will not be recommended for the USPI.

The SMQ (narrow and broad) for peripheral neuropathy for the Pre-Crossover Period of Adult Main Study 301 is presented in the table below.

Table 62. Peripheral Neuropathy, Adult Main Study 301

System Organ Class/ Preferred Term	Original Monovalent[a] N=19735	Placebo[a] N=9847
Total follow-up time post-Dose 1, person-years	6897.6	3641.1
Mean follow-up time post-Dose 1, days	127.7	135.1
Median follow-up time post-Dose 1, days	97	96
Any SMQs (Events), n (rate per 100 person-years), (95% CI)	41 (0.59), (0.43, 0.81)	25 (0.69), (0.44, 1.01)
Number of participants with SMQ, n (%)[b]	36 (0.18)	22 (0.22)
Received Dose 1, n (%)	36 (100.00)	22 (100.00)
Average follow-up time, days	103.3	160.0
Received Dose 2, n (%)	33 (91.67)	22 (100.00)
Average follow-up time, days)	105.5	160.0
Nervous system disorders, n (rate per 100 person-years), (95% CI)	36 (0.52), (0.37, 0.72)	24 (0.66), (0.42, 0.98)
Burning sensation, n (%)	0 (0.00)	2 (0.05)
Hypoesthesia, n (%)	10 (0.14)	8 (0.22)
Neuralgia, n (%)	5 (0.07)	2 (0.05)
Neuropathy peripheral, n (%)	3 (0.04)	3 (0.08)
Paresthesia, n (%)	18 (0.26)	9 (0.25)
Musculoskeletal and connective tissue disorders, n (rate per 100 person-years), (95% CI)	3 (0.04), (0.01, 0.13)	1 (0.03), (0.00, 0.15)
Muscular weakness, n (%)	3 (0.04)	1 (0.03)
Ear and labyrinth disorders, n (rate per 100 person-years), (95% CI)	1 (0.01), (0.00, 0.08)	0 (0.00), (NA, 0.10)
Paresthesia ear, n (%)	1 (0.01)	0 (0.00)
General disorders and administration site conditions, n (rate per 100 person-years), (95% CI)	1 (0.01), (0.00, 0.08)	0 (0.00), (NA, 0.10)
Gait disturbance, n (%)	1 (0.01)	0 (0.00)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Page 4098-4099
Abbreviations: CI=confidence interval; PY=person years; SMQ=Standard Medical Dictionary for Regulated Activities Query
a. Treatment group applicable to period.
b. Percent calculated based on number of participants in safety analysis set in each treatment period.
Note: At the SOC level, the number of events, event rate per 100 PY, and 95% CI for event rate are presented in first row, with the following rows based on participants experiencing events within the SOC. The 95% CI is calculated using the Poisson distribution.
Based on data extract: 2022-11-23. MEDDRA 25.0.

The event rate per 100 person-years for Embolic and Thrombotic events in the vaccine group was 0.59 (95% CI: 0.43, 0.81) versus 0.69 (95% CI: 0.44, 1.01) in the placebo group. These data suggest an imbalance in favor of the placebo group, hence there is no evidence for a peripheral neuropathy safety signal based on this information.

Embolic and Thrombotic Events

The SMQ (narrow and broad) for embolic and thrombotic events for the Pre-Crossover Period of Adult Main Study 301 is presented in the table below.

Table 63. Embolic and Thrombotic Events, Adult Main Study 301

System Organ Class **Preferred Term**	**Original Monovalent[a]** **N=19735**	**Placebo[a]** **N=9847**
Total follow-up time post-Dose 1, person-years	6897.6	3641.1
Mean follow-up time post-Dose 1, days	127.7	135.1
Median follow-up time post-Dose 1, days	97	96
Any SMQs (Events), n (rate per 100 person-years), (95% CI)	40 (0.58), (0.41, 0.79)	17 (0.47), (0.27, 0.75)
Number of participants with SMQ, n (%)[b]	37 (0.19)	15 (0.15)
Received Dose 1, n (%)	37 (100.00)	15 (100.00)
Average follow-up time, days	214.4	156.5
Received Dose 2, n (%)	33 (89.19)	13 (86.67)
Average follow-up time, days	221.7	130.7
Cardiac disorders, n (rate per 100 person-years), (95% CI)	12 (0.17), (0.09, 0.30)	7 (0.19), (0.08, 0.40)
Acute coronary syndrome, n (%)	1 (0.01)	0 (0.00)
Acute myocardial infarction, n (%)	3 (0.04)	4 (0.11)
Coronary artery occlusion, n (%)	1 (0.01)	0 (0.00)
Myocardial infarction, n (%)	6 (0.09)	3 (0.08)
Stress cardiomyopathy, n (%)	1 (0.01)	0 (0.00)
Nervous system disorders, n (rate per 100 person-years), (95% CI)	12 (0.17), (0.09, 0.30)	4 (0.11), (0.03, 0.28)
Cerebellar infarction, n (%)	0 (0.00)	1 (0.03)
Cerebral infarction, n (%)	1 (0.01)	0 (0.00)
Cerebrovascular accident, n (%)	8 (0.12)	1 (0.03)
Hemiparesis, n (%)	0 (0.00)	1 (0.03)
Ischemic stroke, n (%)	1 (0.01)	0 (0.00)
Transient ischemic attack, n (%)	2 (0.03)	1 (0.03)
Vascular disorders, n (rate per 100 person-years), (95% CI)	8 (0.12), (0.05, 0.23)	3 (0.08), (0.02, 0.24)
Deep vein thrombosis, n (%)	3 (0.04)	1 (0.03)
Embolism, n (%)	0 (0.00)	1 (0.03)
Peripheral arterial occlusive disease, n (%)	1 (0.01)	1 (0.03)
Superficial vein thrombosis, n (%)	2 (0.03)	0 (0.00)
Thrombosis, n (%)	2 (0.03)	0 (0.00)
Respiratory, thoracic, and mediastinal disorders, n (rate per 100 person-years), (95% CI)	6 (0.09), (0.03, 0.19)	2 (0.05), (0.01, 0.20)
Pulmonary embolism, n (%)	6 (0.09)	2 (0.05)
Blood and lymphatic system disorders, n (rate per 100 person-years), (95% CI)	1 (0.01), (0.00, 0.08)	0 (0.00), (NA, 0.10)
Splenic infarction, n (%)	1 (0.01)	0 (0.00)
Gastrointestinal disorders	1 (0.01), (0.00, 0.08)	0 (0.00), (NA, 0.10)
Mesenteric artery thrombosis, n (%)	1 (0.01)	0 (0.00)

System Organ Class Preferred Term	Original Monovalent[a] N=19735	Placebo[a] N=9847
General disorders and administration site conditions, n (rate per 100 person-years), (95% CI)	0 (0.00), (NA, 0.05)	1 (0.03), (0.00, 0.15)
Catheter site thrombosis, n (%)	0 (0.00)	1 (0.03)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR, Page 4041-4044
Abbreviations: CI=confidence interval; PY=person years; SMQ=Standard Medical Dictionary for Regulated Activities Query
a. Treatment group applicable to period.
b. Percent calculated based on number of participants in safety analysis set in each treatment period.
Note: At the SOC level, the number of events, event rate per 100 PY, and 95% CI for event rate are presented in first row, with the following rows based on participants experiencing events within the SOC. The 95% CI is calculated using the Poisson distribution.
Based on data extract: 2022-11-23. MEDDRA 25.0.

Clinical Reviewer Comment: The event rate per 100 person-years for Embolic and Thrombotic events in the vaccine group was 0.58 (95% CI: 0.41, 0.79) versus 0.47 (95% CI: 0.27, 0.75) in the placebo group. These data suggest an imbalance; however, this SMQ includes cardiac and neurologic preferred terms that were previously addressed. When non-cardiac, non-neurovascular thrombotic and embolic events were considered, small numerical imbalances were noted, the largest of which was under pulmonary embolism [vaccine n=6 (0.09 (95% CI: 0.03, 0.19))] versus [placebo n=2 (0.05 (95% CI: 0.01, 0.20))]. These data were reviewed under the EUA that supported authorization of the Original Monovalent Wuhan vaccine. Non-cardiac, non-neurovascular thrombotic and embolic events are currently in the EUA Fact Sheet, and nothing has been presented that excludes these events as a safety signal. The clinical reviewer will therefore recommend that the language regarding non-cardiac, non-neurovascular thrombotic and embolic events be placed in the USPI. For further information on the analysis that informed the Fact Sheet labeling, the reader is referred to the original EUA review.

6.1.12.7 Dropouts and/or Discontinuations

AEs Leading to Discontinuation

In the pre-crossover period, the percentage of participants reporting AEs leading to discontinuation of the vaccine were comparable between the Original Monovalent (0.3%) and placebo (0.2%) arms. The most common event leading to discontinuation in the Original Monovalent arm was Pyrexia (n=4, 0.1%). Of the most frequently reported events leading to discontinuation of vaccine (occurring in ≥3 participants) in the Original Monovalent group, most were consistent with systemic reactogenicity (diarrhea, pyrexia, headache, and nausea). Acute kidney injury, cardiac arrest, and cough did not have numeric or percentage imbalances between the vaccine and placebo groups. As discussed above, cerebrovascular accident events are numerically imbalanced in the SAE analysis of the pre-crossover period along with atrial fibrillation, and both imbalances were felt to be clinically significant. The numeric imbalance in cerebrovascular accident events carried over to the adverse event leading to discontinuation analysis. Cerebrovascular event monitoring is also going to be conducted as part of the postmarketing surveillance. Please note that this analysis changed from the original EUA review because COVID-19 events were removed from the AE dataset.[6]

In the post-crossover period, the percentage of participants reporting AEs leading to discontinuation was low and comparable in both treatment groups (Placebo to Original

[6] eSub 3 CSR Addendum to the 2019nCoV-301 Adult 17-Month Report, Table 68, Page 112

Monovalent group 0.1% versus Original Monovalent to Placebo group 0.1%). No preferred term in this analysis occurred in more than 3 participants.

AEs Leading to Study Withdrawal

In the pre-crossover period, the percentage of participants AEs leading to study withdrawal were comparable between the Original Monovalent (0.12%) and placebo (0.12%) groups through the data cutoff date. The most common event leading to study withdrawal in the Original Monovalent group was Cardiac Arrest (Original Monovalent n=5; 0.1% vs Placebo n=3; <0.1%). The percentage of participants who withdrew for this study was generally low, and save for cardiac arrest, did not occur in more than 2 participants.

In the post-crossover period, percentage of participants reporting AEs leading to withdrawal of the vaccine were comparable between the participants who crossed over to receive Original Monovalent (0.2%) and participants who crossed over to receive placebo (0.2%). For participants who crossed over to receive Original Monovalent, there were no events leading to study withdrawal reported by more than 1 participant. The only event leading to withdrawal reported by more than 1 participant who crossed over to receive placebo was death (n=4, >0.1%). Please see section 6.1.12.3 for a further discussion of deaths.

> *Clinical Reviewer Comment: The rates of study withdrawal and study discontinuation were low for the pre- and post-crossover periods and did not adversely affect the study.*

6.1.13 Study Summary and Conclusions

VE against central laboratory-confirmed mild, moderate, or severe COVID-19 over a median follow-up period of 2.5 months after completion of the primary series was 89.7% (95% CI: 82.7, 93.8) for the prevention of PCR-confirmed symptomatic COVID-19 illness diagnosed ≥7 days after completion of the second vaccination. Effectiveness in older adults was further supported by subgroup analyses showing similar neutralizing antibody titers in participants ≥65 years of age [VE of 67.8% (95% CI: -43.0, 92.8)] compared with those 50 through 64 years of age [VE of 89.2% (95% CI: 67.9, 96.4), for whom similar VE was observed compared with the subgroup of participants 18 through 64 years of age [VE of 90.8% (95% CI: 83.9, 94.7)]. Because of the small numbers of cases in the older age strata, this analysis should be considered descriptive and interpreted with caution.

The available safety analysis population consisted of N=29,582, which included 19,735 recipients of at least one dose of the Original Monovalent and 9,847 placebo recipients during the initial vaccination. Local and systemic solicited events were more common after administration of Original Monovalent compared with placebo, with increased frequency and severity following the second dose. The most frequently reported local AR was injection site pain/tenderness. After Original Monovalent vaccination, any Grade 3 local AR was reported by 1.1% of participants post-Dose 1 and 6.2% of participants post-Dose 2. Grade 4 local ARs were only reported following the second dose of Original Monovalent vaccine and occurred in <0.1% of participants. The median time to onset for any local AR was 2 days following vaccination and the median duration was 2-3 days. After Original Monovalent vaccination, Grade 3 and 4 solicited systemic ARs were reported by <3.5% and <0.1% of participants, respectively, post-Dose 1 and by <17.5% and <0.1% of participants, respectively, post-Dose 2. In both treatment groups and for both Dose 1 and Dose 2, fatigue/malaise, headache, and muscle pain (myalgia) were the most commonly reported solicited systemic ARs. For any solicited systemic AR, the median time to onset was 2 days and the median duration was 2 days (range 1-7) for Doses 1 and 2 in both treatment arms.

Multiple events of myocarditis/pericarditis were reported in temporal relationship to Original Monovalent vaccination across pre-market clinical studies, and FDA considers some of these events potentially related to vaccination. Events of lymphadenopathy were infrequent but reported by a higher percentage of participants in the Original Monovalent group, with the highest percentage observed after Dose 2 (0.2%). Hypersensitivity reactions were infrequent among Original Monovalent recipients (0.1%) but were reported at a higher rate than in placebo recipients (0.03%). Additionally, the serious event of angioedema was reported and addressed in the EUA Fact Sheet. Upon further review, it was determined that there was sufficient clinical information to keep angioedema in the USPI. There were several unexplained deaths that were noted during the Blinded Crossover and Booster Vaccination periods. These events were not temporally associated with vaccination, and vaccine relatedness is unlikely. Review of the data also identified several numerical imbalances in specific adverse events of particular interest; these include atrial fibrillation, thromboembolic events, including cardiac and neurovascular events, cholecystitis, uveitis, cardiac failure, and cardiomyopathy. Temporally associated cardiac events were noted during the Blinded Crossover and Booster Vaccination periods. Causality could not be supported by available data. The Applicant's postmarketing surveillance was updated to include atrial fibrillation. Atrial fibrillation, cardiac failure, cardiomyopathy, non-cardiac, non-neurovascular embolic events, uveitis, acute cholecystitis, lymphadenopathy, and myocarditis/ pericarditis will be included in the USPI.

The updated safety information for Adult Main Study 301 supports approval of the vaccine, and the risk-benefit assessment for this vaccine technology remains favorable. The numeric imbalances noted above have been addressed in labeling, and appropriate postmarketing surveillance is being conducted.

6.2 Pediatric Expansion Study 301

NCT04611802

Title: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1 Adjuvant in Adult Participants ≥18 Years With a Pediatric Expansion in Adolescents (12 to <18 Years)

6.2.1 Objectives

The objectives and endpoints for evaluating the safety and efficacy of the 3rd vaccine dose in individuals 12 through 17 years of age who had previously received two doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) were:

Primary Immunogenicity Objectives

- To describe the humoral immune response at 28 days post Dose 3 of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in terms of neutralizing antibody to SARS-CoV-2 for all Immunogenicity Population participants, and for subsets with and without prior SARS-CoV-2 exposure determined by detectable pre-Dose 3 anti-NP antibodies.
- To assess the immune response at 28 days post Dose 3 by IgG antibody to SARS-CoV-2 S protein and hACE2 inhibition titers in all Immunogenicity Population participants, and for subsets with and without pre-dose SARS-CoV-2 exposure determined by detectable anti-NP antibodies. To assess the level of humoral immune response post Dose 3 in comparison with that after completion of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

- Safety Objectives
- To describe the safety experience for the vaccine in adolescent participants based on solicited short-term reactogenicity by toxicity grade for days after Dose 3.
- To assess overall safety through 28 days after Dose 3.
- To assess the frequency and severity of MAAEs attributed to vaccine, AESIs, or SAEs through EoS.
- To assess all-cause mortality after Dose 3.

6.2.2 Design Overview

Pediatric Expansion Study 301 was a randomized, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adolescents 12 years through 17 years of age. Approximately 3,000 adolescents were enrolled from U.S. study sites and randomized in a 2:1 ratio via block randomization to receive 2 intramuscular injections of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or placebo (normal saline) 3 weeks apart. Following blinded crossover, 2 doses of the other study drug were administered 21 days apart.

In response to the evolving pandemic and related public health recommendations, Novavax modified the protocol for Pediatric Extension Study 301 to evaluate a 3rd ("booster") dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age, no less than 5 months after completion of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Dose 3 cohorts were defined by the 2-dose treatment received prior to blinded crossover [i.e., Cohort 2 received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) prior to crossover to placebo and Cohort 1 received placebo prior to crossover to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)]. A total of 1,499 adolescents received a 3rd dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

6.2.3 Population

The Pediatric Expansion enrolled vaccine-naïve adolescents 12 to <18 years of age at screening, determined to be healthy or medically stable by the investigator who were willing and able to give informed consent and assent, as required, prior to study enrollment and to comply with study procedures, and agreed to not enroll in another SARS-CoV-2 prevention trial during the study follow-up.

Pertinent Exclusion Criteria

History of a previous laboratory-confirmed diagnosis of SARS-CoV-2 infection or COVID-19. A previous diagnosis of COVID-19 during participation in this trial is not exclusionary for the Booster Amendment.

Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) or therapy that causes clinically significant immunosuppression.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The Novavax Prototype vaccine is a SARS-CoV-2 recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) constructed from the full-length, wild-type SARS-CoV-2 S glycoprotein (based on Wuhan-Hu-1 isolate). The SARS-CoV-2 rS vaccine is administered with

Matrix-MTM adjuvant (previously referred to as Matrix M1), a saponin-based adjuvant developed at Novavax AB (Uppsala, Sweden) and derived from fractionated *Quillaja* saponins, phosphatidylcholine, and cholesterol.

Placebo was sterile normal saline (0.9% sodium chloride in water).

6.2.5 Directions for Use

Two intramuscular injections (Dose 1 and Dose 2) of either Original Monovalent (containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) or saline placebo were administered 21 days apart, at Day 0 and Day 21 (vaccination window of up to +7 days).

6.2.6 Sites and Centers

Participants were enrolled at 73 clinical sites in the U.S.

6.2.7 Surveillance/Monitoring

Efficacy

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 receptor binding inhibition) were collected from all enrolled participants before vaccination and at appointed time points following vaccination. Blood samples were obtained during the immediate period after the first set of vaccinations only (Day 0, 21 and 35), and were to be obtained in the long-term (at selected subsequent time points until Month 24) follow-up of all participants.

Blood samples for serologic assessments (anti-NP antibodies, IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 receptor binding inhibition) in the booster vaccination period were collected from all participants prior to the booster vaccination and 28 days after receiving the booster vaccination. While the time between the assessment of immune responses after the primary vaccination series (14 days) and after the booster dose (28 days) differed, this was not expected to have a notable impact on evaluation of the booster dose and may, in fact, underestimate the relative immunogenicity of the booster doses. Immune measurements (IgG antibody to SARS-CoV-2 S protein, MN, and hACE2 inhibition) were performed on all adolescent participants from the active and placebo treatment groups split approximately evenly across the two age categories, designated at random by biostatisticians who were blinded to treatment assignment. Testing for anti-NP antibodies was performed on serum from all available enrolled participants to evaluate prior infection at baseline and new infection (including asymptomatic infection) across the duration of the study. Whole blood samples for PBMC testing for cell-mediated immunity were collected at Days 0, 7, and 28 from a small subset of participants comprised of 50 adolescent participants representing both age strata and reasonably reflecting the demographic subgroups enrolled at selected study sites with the capacity to isolate PBMCs. These study sites were identified prior to trial initiation. No PBMCs were collected following the booster vaccination.

All AEs reported or observed by study staff during the study were recorded on the AE page of the electronic case report form. All AEs were coded according to the latest version of MedDRA.

On vaccination days, participants remained in clinic (or under observation) for at least 30 minutes to be observed for any immediate reaction. Site specific local (arm) and general systemic reactogenicity reactions including start and stop dates were recorded following the

initial set of vaccinations and the investigator applied a standard toxicology grading at the subsequent study visit. Any immediate reactions were recorded as AEs on day of vaccination.

Participants used their eDiary to record reactogenicity following vaccination, starting on the same day of vaccination for a total of 7 days. If a local or systemic solicited adverse event extended beyond 7 days after vaccination (toxicity Grade ≥1), then it was recorded as an AE with a start date that matched Day 7 of the reactogenicity event and was followed to resolution per FDA guidelines for AE capture. At any time after Day 0, severe COVID-19 (as defined in Section 6.2.8) would have been reported as an SAE.

All unsolicited AEs of any severity were collected from the time of first study vaccination through 28 days after the second injection of each set of vaccinations (initial and crossover) and from the time of vaccination through 28 days after the booster injection. Any relevant observations made prior to the first dose of trial vaccine were recorded on the AE electronic case report form but were not to be considered AEs. All AEs were coded according to MedDRA Version 25.0.

MAAEs were collected from the time of first study vaccination through 28 days after second injection of each set of vaccinations (initial and crossover) and through 28 days after booster vaccination, and MAAEs attributed to vaccine were collected from the time of first study vaccination (initial, crossover, and booster) through the data cutoff date August 6, 2022.

All SAEs and AESIs were collected from signing of informed consent through the data cutoff date. AESIs included PIMMCs, AEs specific to complications of COVID-19, or other potential AEs that may have been determined at any time by regulatory authorities as additional information concerning COVID-19 was obtained. Safety was monitored on an ongoing basis by the Data and Safety Monitoring Board.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint:

- First episode of PCR-positive mild, moderate, or severe COVID-19, where severity was defined as:

Mild COVID-19 (≥1 of the following):

- Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
- New onset cough
- ≥2 additional COVID-19 symptoms:
    - New onset or worsening of shortness of breath or difficulty breathing compared with baseline
    - New onset fatigue
    - New onset generalized muscle or body aches
    - New onset headache
    - New loss of taste or smell
    - Acute onset of sore throat, congestion, or runny nose
    - New onset nausea, vomiting, or diarrhea

OR Moderate COVID-19 (≥1 of the following):

- High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days).
- Any evidence of significant LRTI:
    - Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline)
    - Tachypnea: 24 to 29 breaths per minute at rest
    - SpO_2: 94% to 95% on room air
    - Abnormal chest X-ray or chest CT consistent with pneumonia or LRTI
- Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor).

OR Severe COVID-19 (≥1 of the following):

- Tachypnea: ≥30 breaths per minute at rest.
- Resting heart rate ≥125 beats per minute.
- SpO_2: ≥93% on room air or PaO_2/FiO_2 <300 mmHg.
- High flow oxygen (O_2) therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure).
- Mechanical ventilation or ECMO.
- One or more major organ system dysfunction or failure to be defined by diagnostic testing/clinical syndrome/interventions, including any of the following:
    - Acute respiratory failure, including acute respiratory distress syndrome
    - Acute renal failure
    - Acute hepatic failure
    - Acute right or left heart failure
    - Septic or cardiogenic shock (with shock defined as systolic blood pressure <90 mm Hg OR diastolic blood pressure <60 mm Hg)
    - Acute stroke (ischemic or hemorrhagic)
    - Acute thrombotic event: acute myocardial infarction, DVT, PE
    - Requirement for: vasopressors, systemic corticosteroids, or hemodialysis
- Multisystem Inflammatory Syndrome in Children (MIS-C), as per the CDC definition:
    - An individual <21 years of age presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: elevated C-reactive protein, erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactate dehydrogenase (LDH), or IL-6; elevated neutrophils; reduced lymphocytes; low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND

- No alternative plausible diagnoses;

AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

- Admission to an ICU.
- Death.

Key Secondary Endpoint:

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

Other Secondary Endpoints:

- First episode of PCR-positive moderate or severe COVID-19, as defined under the primary endpoint.
- ANY symptomatic SARS-CoV-2 infection, defined as: PCR-positive nasal swab and ≥1 of any of the following symptoms:
  - Fever.
  - New onset cough.
  - New onset or worsening of shortness of breath or difficulty breathing compared to baseline.
  - New onset fatigue.
  - New onset generalized muscle or body aches.
  - New onset headache.
  - New loss of taste or smell.
  - Acute onset of sore throat, congestion, or runny nose.
  - New onset nausea, vomiting, or diarrhea.
- Percentage of adolescent participants reporting SARS-CoV-2 infection (COVID-19) from Day 28 through end of Year 1, with severity classification as defined in the Adult Main Study (mild, moderate, or severe).
- Neutralizing antibody response at Day 35 by age strata (12 to X and X to <18) and with and without anti-SARS-CoV-2 NP antibodies at baseline, compared with that observed in adult participants 18 to <26 years of age from the Adult Main Study (Immunogenicity Population participants before crossover).
- Antibodies to SARS-CoV-2 NP at Days 0 and 35, and at specified time points until Month 24 were to be used to determine natural infection and to determine the incidence of undiagnosed infection acquired during study follow-up. Serum IgG levels to SARS-CoV-2 S protein, hACE2 inhibition titers 14 days after second injection of the initial vaccination series (Day 35) in adolescent participants and subsets with and without anti-NP antibodies at baseline.

- Serum IgG levels to SARS-CoV-2 S protein, MN_{50}, and hACE2 inhibition titers at specified time points until Month 24.
- Description of course, treatment and severity of COVID-19 reported after a PCR-confirmed case via the Endpoint Form.
- Antibodies to SARS-CoV-2 NP, regardless of whether the infection was symptomatic.

Safety Endpoints:

- Reactogenicity incidence, duration, and severity (mild, moderate, or severe) recorded by parent(s)/caregiver(s) on their electronic patient-reported outcome diary application (eDiary) on days of vaccination and subsequent 6 days (total 7 days after each vaccine injection in the initial set of vaccinations).
    - Reactogenicity injection site reactions:
        - Pain
        - Tenderness
        - Erythema
        - Swelling/induration
    - Systemic reactions:
        - Fever
        - Malaise
        - Fatigue
        - Arthralgia
        - Myalgia
        - Headache
        - Nausea/vomiting
- Incidence and severity of MAAEs through 49 days, i.e., 28 days after second injection of each set of vaccinations (initial and crossover).
- Incidence and severity of unsolicited AEs through 49 days, i.e., 28 days after second injection of each set of vaccinations (initial and crossover).
- Incidence and severity of MAAEs attributed to trial vaccine, SAEs and AESIs through Month 12.
- Incidence and severity of SAEs (including COVID-19 diagnoses), MAAEs attributed to trial vaccine and AESIs during Month 12 through Month 24 or the EoS.
- Death due to any cause.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Initial Vaccination Period

The sample size for the **Pediatric Expansion** was chosen to provide an adequate safety database of ≥2,000 pediatric recipients of investigational product to support licensure of the SARS-CoV-2 rS Matrix-adjuvanted vaccine in pediatric participants 12 to <18 years of age.

Recruitment of study participants attempted to enroll a similar number of participants in the 12 to <15 and 15 to <18 years of age groups. With 2,000 participants in the active vaccine group, there was a >90% probability of observing at least 1 participant with an AE if the true incidence of the AE was 0.12% and a 99% probability if the true incidence of the AE was 0.23%.

The enrollment of approximately 3,000 adolescent participants with a 2:1 randomization to active vaccine or placebo provided a total of approximately 2,000 pediatric participants exposed to active vaccine.

The analysis of efficacy in the Pediatric Expansion was descriptive in nature using the same methods as the Adult Main Study but with no formal statistical hypothesis tested.

The blinded crossover ~6 months after completion of the initial vaccine series and 12 months of follow-up after crossover were aimed to collect ≥12 months of safety data after receipt of the active adjuvanted vaccine.

A non-randomized noninferiority (NI) analysis of immunogenicity was performed between the adolescents in the **Pediatric Expansion** of the study and the 18 to <26 years of age adult population in the **Adult Main Study**.

A sample of 750 participants was randomly selected from the **Pediatric Expansion** for testing of neutralization titers, which provided approximately 400 participants for the NI analysis, accounting for the 2:1 randomization and 20% non-evaluability. Similarly, a separate random sample of 750 participants 18 to <26 years of age from the **Adult Main Study** was drawn to provide approximately 400 participants for the NI analysis, accounting for the 2:1 randomization and 20% non-evaluability.

For the effectiveness endpoint, successful demonstration of noninferiority required meeting the following 3 pre-specified criteria simultaneously,

1. lower bound of two-sided 95% CI for the ratio of GMTs (GMT18-<26yo/GMT12-<18yo) >0.67 (estimated as 1/1.5),
2. point estimate of the ratio of GMTs ≥0.82 (estimated as square root of 1/1.5)
3. lower bound of the 2-sided 95% CI for difference of seroresponse rates (SRR12-<18yo–SRR18-<26yo) was >-10%

These criteria can also be presented using the adolescents as the reference group, as such:

1. upper bound of two-sided 95% CI for the ratio of GMTs ($GMT_{12-<18yo}/GMT_{18-<26yo}$) <1.5,
2. point estimate of the ratio of GMTs ≤1.22 (estimated as square root of 1/1.5)
3. upper bound of the two-sided 95% CI for difference of seroresponse rates ($SRR_{12-<18yo} - SRR_{18-<26yo}$) was <10%

With 400 evaluable participants (500 accounting for 20% non-evaluability) in the active vaccine group randomly selected from each of the 18 to <26 years of age subset of participants in the **Adult Main Study** and the **Pediatric Expansion**, there was over 85% power (through simulations) to demonstrate the first 2 noninferiority criteria when assuming an underlying GMT for the 18 to <26 years of age group up to 1.1-fold higher than the 12 to <18 years of age group.

Booster Vaccination Period

To evaluate the immunogenicity of booster vaccine regimens with Original Monovalent in adolescent participants, two statistical hypotheses were evaluated. Testing was performed using the results of the analysis of neutralizing antibody titers against the wild-type virus (ancestral Wuhan strain) (GMFR and difference of SCRs) in Cohort 2. Other analyses were descriptive. The hypotheses tested were as follows:

Noninferiority of a single booster dose of Original Monovalent, as measured by the LB of the 95% CI for the ratio of MN_{50} GMT 28 days after a single booster dose versus 14 days after 2nd active dose being >1.0. Expressed statistically as:

H0: $GMT_{booster}/GMT_{D35} \leq 1.0$
H1: $GMT_{booster}/GMT_{D35} > 1.0$

Noninferiority of a single booster dose of Original Monovalent, as measured by the LB of the 95% exact CI for the difference of percentage of participants with SCR in MN_{50} titers 28 days after a single booster dose relative to the time of the first dose of Original Monovalent versus 14 days after the second dose of Original Monovalent relative to the time of the first dose of Original Monovalent being >-10%. Expressed statistically as:

H0: $SCR_{booster}/SCR_{D35} \leq -10\%$
H1: $SCR_{booster}/SCR_{D35} > -10\%$

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The **Intent-To-Treat (ITT) Analysis Set** included all participants who were randomized, regardless of protocol violations or missing data. The ITT analysis set was used for participant disposition summaries and was analyzed according to the treatment arm to which the participant was randomized.

The **Full Analysis Set (FAS)** included all participants who were randomized and received at least 1 dose of trial vaccine/placebo, regardless of protocol violations or missing data. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. Participants in the blinded- crossover phase were censored at the time of the receipt of vaccine/placebo. The FAS population was analyzed according to the treatment group to which they were randomized. The FAS analysis sets were used for supportive analyses. When the efficacy endpoints were analyzed using FAS, baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity was ignored.

The **Safety Analysis Set** included all participants who received at least 1 dose of trial vaccine. Participants in the Safety Analysis Set were analyzed according to the treatment actually received. In cases where information was available that indicated that a participant received both active and placebo vaccine during the initial or crossover period, the participant was analyzed as part of the active group. Presentations specific to solicited reactogenicity events are limited to participants in the Safety Analysis Set who entered data into the eDiary for the relevant dose.

- **The Booster Safety Analysis Set** includes all participants in the safety analysis set who received a dose during the booster portion of the study. Some safety analyses are presented by the treatment that was received in the initial period of the study, labeled as

"Cohort 1" and "Cohort 2". The booster safety analysis set Cohort 1 includes all boosted participants who received placebo during the initial period and were planned to receive SARS-CoV-2 in the blinded crossover period. The booster safety analysis set Cohort 2 includes all boosted participants who received SARS-CoV-2 in the initial period.

Per-Protocol Analysis Sets for Efficacy Analyses - Per-protocol sets for different analyses are defined below. The review and determination for exclusion from the PP-EFF and PP-EFF-2 analysis sets was carried out in a blinded fashion by a study clinician prior to unblinding for the analysis based on all available information from the locked database. Other per-protocol analysis sets were determined in a blinded fashion, but post unblinding for the initial analysis performed for Emergency Use Authorization.

- The **PP-EFF** analysis set included all participants who received the full regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (i.e., participant was censored at the time of the protocol deviation) and that were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity. Participants who were unblinded with an intention to receive other COVID-19 vaccines were censored at the time of unblinding. Although the study enrolled participants regardless of SARS-CoV-2 serologic status at the time of initial vaccination, any participants with confirmed infection or prior infection due to SARS-CoV-2 at baseline, by nasal swab PCR or serology, were excluded from the PP-EFF population. Participants censored prior to the start of the observation period were excluded from PP-EFF. PP-EFF was the primary set for all efficacy endpoints.
- A second per-protocol efficacy analysis set (**PP-EFF-2**) was defined to allow for evaluation of baseline positivity's impact on vaccine efficacy, either seropositivity (determined by anti-NP antibody test) or virological positivity (determined by PCR). The PP-EFF-2 analysis set followed the same method described in the PP-EFF population with the exception that it included all participants regardless of baseline status.
- A third per-protocol efficacy (**PP-EFF-3**) analysis set was defined for the evaluation of VE post-crossover. This efficacy analysis was expected to occur prior to the first adolescent participant being offered a booster dose (i.e., third dose of active vaccine). The PP-EFF-3 set included participants who were part of PP- EFF who had no prior PCR-confirmed SARS-CoV-2 infection in the pre- crossover period, who had no prior SARS-CoV-2 infection by positive anti-NP antibody test or positive nasal swab PCR prior to the time of first crossover dose, who received 2 crossover doses with the second dose administered within 60 days of the first dose, and who remained SARS-CoV-2 negative by PCR prior to 7 days after the second dose.
- A fourth per-protocol efficacy-like (**PP-UNDIAG**) analysis set was defined for the evaluation of undiagnosed infection using anti-NP and the nasal swab taken immediately prior to administering the first crossover dose. Participants in this population received the full regimen of trial vaccine during the initial series, had results for all scheduled anti-NP blood draws up to and including the crossover visit, were not baseline positive (by anti-NP or PCR) and had no censoring case prior to Day 35 anti-NP measurement. Censoring cases included major protocol deviation, withdrawal from study, unblinding, or evidence of a positive PCR result (whether for symptomatic COVID-19 episode or asymptomatic).

Per-Protocol Sets for Immunogenicity Analyses – The Per-Protocol Set for Immunogenicity Analyses (PP-IMM) analysis set for the main immunogenicity analysis was determined for each study visit and may have been assay specific (i.e., serum vs PBMC). The PP-IMM analysis set

included participants that had at least a baseline and 1 serum sample result available after vaccination and no major protocol violations that were considered clinically relevant to impact immunological measures at the visit in question. The PP-IMM analysis set excluded participants who had a PCR positive nasal swab between baseline up to the visit analyzed.

- All participants in the **PP-IMM** analysis population were designated at time of vaccination within the immunogenicity subset. For participant visits on or after Day 21, participants had to receive the second vaccination to be included in the PP-IMM analysis set. Prior exposed participants were determined using baseline SARS-CoV-2 nasal swab or seropositivity at screening and excluded from PP- IMM analysis set.
- A second per-protocol immunogenicity (**PP-IMM-2**) analysis set was defined to allow for evaluation of baseline positivity (either by anti-NP or PCR) on immunogenicity population participants for the main immunogenicity analysis. The PP-IMM-2 analysis set followed the same method described in PP-IMM population with the exception that it included all participants regardless of baseline status.
- **Booster Per-Protocol Immunogenicity Analysis Set** - included participants who received 2 doses of the active vaccine either in the initial vaccination period or in the blinded crossover vaccination period, had an immunogenicity blood sample collected at Day 35 after the primary series, did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose, did not receive an emergency use authorized COVID-19 vaccine, received the booster dose, and did not have major protocol deviations or unblind through 7 days post-crossover Dose 2. Participants in the booster per-protocol immunogenicity (booster PP-IMM) analysis set were determined for each study visit and may be assay specific (i.e., serum), which includes participants that had serum sample results available at tested visits and analyzed as outlined below. Participants who were included in Cohort 1 or 2 were also included in the combined cohort analysis of results. The analysis of the combined cohorts only included visits that were tested for both cohorts as outlined in the SAP.

6.2.10.1.1 Demographics

The table below summarizes demographic representation of study participants who enrolled in Pediatric Expansion Study 301 and were randomized to a two-dose series of Original Monovalent or placebo.

Table 64. Demographics and Baseline Characteristics for the Pre-Crossover Vaccination Period, Per Protocol Efficacy Set, Pediatric Expansion Study 301

Characteristic	Original Monovalent N=1199	Placebo N=589	Total N=1788
Age (years)	--	--	--
Mean (SD)	13.8 (1.39)	13.7 (1.41)	13.8 (1.40)
Median	14	14	14
Minimum, maximum	12, 17	12, 17	12, 17
Age group, n (%)	--	--	--
12 to <15 years	818 (68.2)	404 (68.6)	1222 (68.3)
15 to <18 years	381 (31.8)	185 (31.4)	566 (31.7)
Sex, n (%)	--	--	--
Male	618 (51.5)	324 (55.0)	942 (52.7)
Female	581 (48.5)	265 (45.0)	846 (47.3)

Characteristic	Original Monovalent N=1199	Placebo N=589	Total N=1788
Race, n (%)	--	--	--
White	920 (76.7)	444 (75.4)	1364 (76.3)
Black or African American	153 (12.8)	77 (13.1)	230 (12.9)
American Indian or Alaska Native[a]	13 (1.1)	6 (1.0)	19 (1.1)
Asian	37 (3.1)	24 (4.1)	61 (3.4)
Mixed origin	66 (5.5)	33 (5.6)	99 (5.5)
Native Hawaiian or other Pacific Islander	3 (0.3)	1 (0.2)	4 (0.2)
Not reported	7 (0.6)	4 (0.7)	11 (0.6)
Ethnicity, n (%)	--	--	--
Not Hispanic or Latino	1007 (84.0)	489 (83.0)	1496 (83.7)
Hispanic or Latino	187 (15.6)	100 (17.0)	287 (16.1)
Not reported[b]	2 (0.2)	0	2 (0.1)
Unknown	3 (0.3)	0	3 (0.2)
Student attending school in person, n (%)	--	--	--
Yes	833 (69.5)	421 (71.5)	1254 (70.1)
No	366 (30.5)	168 (28.5)	534 (29.9)
Height (cm)	--	--	--
Mean (SD)	164.89 (10.338)	164.35 (10.241)	164.71 (10.306)
Median	165	164	164.92
Minimum, maximum	98.6, 195.6	124.5, 193.0	98.6, 195.6
Weight (kg)	--	--	--
Mean (SD)	65.84 (21.098)	63.40 (20.137)	65.04 (20.812)
Median	61.32	58.50	60.14
Minimum, maximum	30.3, 154.2	26.0, 173.8	26.0, 173.8
BMI (kg/m^2)	--	--	--
Mean (SD)	24.03 (6.682)	23.32 (6.578)	23.79 (6.655)
Median	22.5	21.60	22.1
Minimum, maximum	14.0, 53.0	10.0, 63.8	10.0, 63.8
BMI category, n (%)[c]	--	--	--
Underweight	35 (2.9)	26 (4.4)	61 (3.4)
Healthy weight	627 (52.3)	340 (57.7)	967 (54.1)
Overweight	224 (18.7)	84 (14.3)	308 (17.2)
Obese	313 (26.1)	139 (23.6)	452 (25.3)
Anti-NP/ PCR[d], n (%)	--	--	--
Positive	0	0	0
Negative	1199 (100)	589 (100)	1788 (100)
Missing	0	0	0

Source: Table 6 Page 25, 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR Abbreviations: Anti-NP=anti-nucleoprotein; BMI=body mass index; eCRF=electronic case report form; PCR=polymerase chain reaction; SD=standard deviation; N=The PP-EFF analysis. included all participants who received the full regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (i.e., participant was censored at the time of the protocol deviation) and that were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity; n=number of unique subjects in each category; kg/m^2=kilogram per square meter

a. American Indians were denoted as Native Americans in the eCRF.

b. Original numbers for this category were incorrectly applied from the source table.

c. BMI will be classified as follows (using sex and age specific percentiles): Underweight=participants less than the 5th percentile; Healthy weight=participants within the 5th percentile and up to the 85th percentile; Overweight=participants within the 85th percentile to less than the 95th percentile; Obesity=participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.

d. Participants with either anti-NP or PCR are reported.

Demographics and baseline characteristics of participants in the PP-EFF were well balanced between the Original Monovalent and placebo groups. The overall median age was 14.0 years,

with a range of 12 to 17 years. Approximately 32% were 15 to <18 years of age and approximately half (47.3%) were female. The majority (76.3%) were White, not of Hispanic or Latino origin (83.7%). More than half of participants were of healthy weight (54.1%).

The table below summarizes demographic representation of study participants who enrolled in Pediatric Expansion Study 301 who received a third dose of the vaccine.

Table 65. Demographics and Other Baseline Characteristics for Participants in the Booster Vaccination Period, Booster Safety Analysis Set, Pediatric Expansion Study 301

Characteristic	Cohort 1[a] N=490	Cohort 2[b] N=1009	Total Boosted[c] N=1499
Age (years)	--	--	--
Mean (SD)	13.8 (1.43)	13.8 (1.40)	13.8 (1.41)
Median	14.0	14.0	14.0
Minimum, maximum	12, 17	12, 17	12, 17
Age group, n (%)	--	--	--
12 to <15 years	335 (68.4)	685 (67.9)	1020 (68.0)
15 to <18 years	155 (31.6)	324 (32.1)	479 (32.0)
Sex, n (%)	--	--	--
Male	287 (58.6)	519 (51.4)	806 (53.8)
Female	203 (41.4)	490 (48.6)	693 (46.2)
Race, n (%)	--	--	--
White	354 (72.2)	742 (73.5)	1096 (73.1)
Black or African American	73 (14.9)	146 (14.5)	219 (14.6)
American Indian or Alaska Native	12 (2.4)	28 (2.8)	40 (2.7)
Asian	20 (4.1)	33 (3.3)	53 (3.5)
Mixed origin	25 (5.1)	52 (5.2)	77 (5.1)
Native Hawaiian or other Pacific Islander	2 (0.4)	3 (0.3)	5 (0.3)
Not reported	4 (0.8)	5 (0.5)	9 (0.6)
Ethnicity, n (%)	--	--	--
Hispanic or Latino	84 (17.1)	192 (19.0)	276 (18.4)
Not Hispanic or Latino	406 (82.9)	814 (80.7)	1220 (81.4)
Not reported	0	1 (<0.1)	1 (<0.1)
Unknown	0	2 (0.2)	2 (0.1)
BMI (kg/m^2)	--	--	--
Mean (SD)	23.67 (6.886)	24.77 (7.237)	24.41 (7.141)
Median	21.85	23.10	22.80
Minimum, maximum	10.3, 63.8	14.0, 59.4	10.3, 63.8
BMI category[d], n (%)	--	--	--
Underweight	23 (4.7)	25 (2.5)	48 (3.2)
Healthy weight	272 (55.5)	487 (48.3)	759 (50.6)
Overweight	62 (12.7)	193 (19.1)	255 (17.0)
Obese	133 (27.1)	304 (30.1)	437 (29.2)
Student attending school in person, n (%)	--	--	--
Yes	345 (70.4)	705 (69.9)	1050 (70.0)
No	145 (29.6)	304 (30.1)	449 (30.0)
Anti NP/PCR[e], n (%)	--	--	--
Positive	324 (66.1)	689 (68.3)	1013 (67.6)
Negative	163 (33.3)	314 (31.1)	477 (31.8)
Missing	3 (0.6)	6 (0.6)	9 (0.6)

Source: 2019nCoV-301: 6-Month Booster Safety Addendum to the 12-Month Adolescent Clinical Study Report Pages 22-23, Table 7.Abbreviations: anti-NP=anti-nucleoprotein; BMI=body mass index; PCR=polymerase chain reaction; SD=standard deviation;

N=The Booster Safety Analysis Set, includes all participants in the safety analysis set who received a dose during the booster portion of the study.; n=number of unique subjects in each category; kg/m2=kilogram per square meter.
a. Comprised participants who had received primary series vaccination with Original Monovalent during the blinded crossover vaccination period (median duration [range] between the time of the second dose of Original Monovalent in the blinded crossover vaccination period and the time of booster vaccination with Original Monovalent was 7.6 months [6 to 8 months]).
b. Comprised participants who had received primary series vaccination with Original Monovalent during the initial vaccination period (the median duration [range] between the second dose of Original Monovalent in the initial vaccination period and the time of booster vaccination with Original Monovalent was 10.6 months [9 to 12 months]).
c. Comprised participants in Cohort 1 and Cohort 2 combined (the median [range] between the second dose of Original Monovalent in either the initial vaccination period or blinded crossover vaccination period and the time of booster vaccination with Original Monovalent was 10.3 months [range 6 to 12 months]).
d. BMI was classified as follows (using sex and age specific percentiles): Underweight=participants less than the 5th percentile; Healthy weight=participants within the 5th percentile and up to the 85th percentile; Overweight=participants within the 85th percentile to less than the 95th percentile; Obesity=participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.
e. Participants with either anti-NP or PCR were reported.

The demographics of participants in the booster vaccination period were similar to those enrolled in the initial and blinded crossover vaccination periods. Median age (range) of the Booster Safety Analysis Set was 14.0 years (12 to 17 years), with the majority of participants 12 to <15 years of age. More than half the participants were male, and most were White and not of Hispanic or Latino origin. More than half the participants were of healthy weight, with less than a third of participants obese.

The various demographic subgroups were generally balanced between the vaccine and placebo groups.

6.2.10.1.3 Participant Disposition

The percentages of participants who discontinued from the Initial Vaccination Period were generally balanced between the treatment groups in this study. The most common reason for early termination was withdrawal by participant (Original Monovalent 10.4% versus 13.5% Placebo).

The percentages of participants who discontinued early from the Blinded Crossover Vaccination Period early were generally balanced between the treatment groups in this study. The majority of the participants completed Dose 4 (98.8%). There were no notable trends differing from the discontinuations seen in the Initial Vaccination Period.

The percentages of participants who discontinued early from the Booster Vaccination Period were low (0.4 - 2.7%) and comparable to the other study periods.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

At the time of the data cutoff date (August 6, 2022), a total of 20 cases of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in the pre-crossover (initial) vaccination period were reported accrued. Of these cases, 6 (0.5%) were in the Original Monovalent group and 14 (2.4%) were in the placebo group. All 6 cases in the Original Monovalent group were mild in severity; 13 cases in the placebo group were mild and 1 case was moderate in severity. The VE of Original Monovalent to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative adolescent participants was 79.8% (95% CI: 47.6, 92.2). See table below.

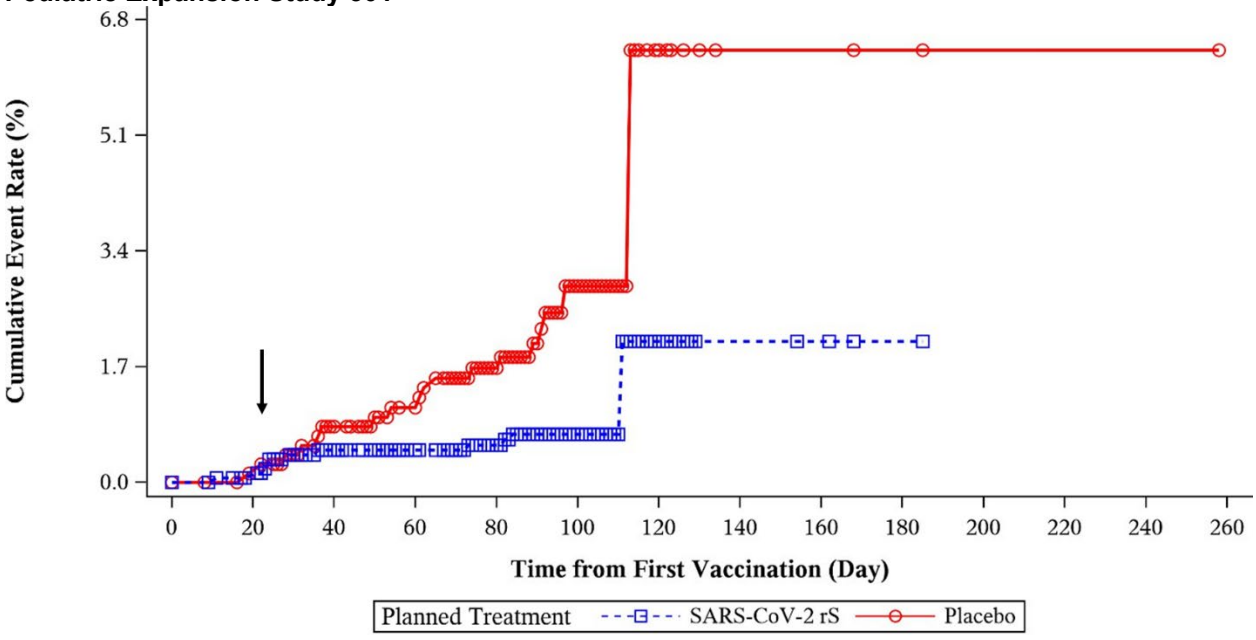
Table 66. Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 With Onset From at Least 7 Days After Second Vaccination of the Pre-Crossover Vaccination Period, PP-EFF Analysis Set, Pediatric Expansion Study 301

Parameter	Original Monovalent N=1199	Placebo N=589
Participants with no occurrence of event[a], n (%)	1193 (99.5)	575 (97.6)
Participants with occurrence of event[b], n (%)	6 (0.5)	14 (2.4)
Severity of first occurrence, n (%)	--	--
Mild	6 (0.5)	13 (2.2)
Moderate	0	1 (0.2)
Severe	0	0
Median surveillance time[c] (days)	--	--
Mean (SD)	63.3 (20.7)	60.6 (15.7)
Median	64.0	63.0
Minimum-maximum	1 - 379	1 - 153
Log-linear model using modified Poisson regression[d]	--	--
Mean Disease Incidence Rate (/100-person year)	2.9	14.3
95% CI	1.3, 6.4	8.5, 24.1
Relative risk	0.2	--
95% CI	0.1, 0.5	--
Vaccine efficacy (%)	**79.8**	--
95% CI	**47.6, 92.2**	--

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR Table 8, page 29
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy; VE=vaccine efficacy; N=The PP-EFF analysis, included all participants who received the full regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (i.e., participant was censored at the time of the protocol deviation) and that were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity; n=number of unique subjects in each category; SD=standard deviation.
a. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria.
b. Event=First occurrence of PCR-Confirmed Mild, Moderate or Severe COVID-19 with onset from 7 days after the second injection within the surveillance period.
c. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of event/ censoring) and date at start of surveillance period (7 days after the Second Injection) + 1. Participants were censored at the earliest of (i)cut-off date (06 August 2022), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) end of follow-up, (vi) first dose of crossover, or (vii) booster dose.
d. Modified Poisson regression with logarithmic link function, treatment group as fixed effect and robust error variance [Zou 2004].

Among those adolescent participants who received at least 1 dose of trial vaccine, regardless of baseline serostatus, there were a total of 29 cases of PCR-confirmed symptomatic mild, moderate or severe COVID-19 with onset from first vaccination of the initial vaccination period, with 11 (0.7%) in the Original Monovalent group and 18 (2.4%) in the placebo group (Figure 2). Cumulative rates of PCR-confirmed symptomatic mild, moderate, and severe COVID-19 began to diverge between 28 days and 3 months after first vaccination.

Figure 2. Cumulative Incidence Curve of PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From First Vaccination of the Initial Vaccination Period in Adolescent Participants Who Received at Least 1 Dose of Trial Vaccine Regardless of Baseline Serostatus, Full Analysis Set, Pediatric Expansion Study 301



No. with events/No. at risk at timepoint

SARS-CoV-2 rS	0 / 1484	1 / 1478	7 / 1440	7 / 1411	8 / 1279	10 / 314	11 / 33	11 / 12	11 / 11	11 / 9	11 / 8	11 / 8	11 / 8	11 / 8
Placebo	0 / 748	1 / 745	6 / 714	8 / 690	12 / 617	17 / 149	18 / 15	18 / 5	18 / 5	18 / 4	18 / 3	18 / 3	18 / 3	18 / 2

Source: Figure 1, page 134 of 2019nCoV-301: 12-Month Adolescent Report
Abbreviations: COVID-19=coronavirus disease 2019; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.
Note: SARS-CoV-2 rS in figure represents Original Monovalent (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant)
Note: Case=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset from first injection within the surveillance period, which was defined as first vaccination through the date of data cut or censoring event.
Note: Participants were censored at the earliest of (i) cutoff date (06 August 2022); 2(ii) date of death; 3(iii) date of unblinding (including for intended receipt of alternative COVID-19 vaccine); (iv4) end of follow-up or; (v5) first dose of crossover; or (vi) first booster dose.
Arrow represents when the second dose was administered, 21 days after first dose.

Clinical Reviewer Comment: Because Pediatric Expansion Study 301 was not powered to demonstrate efficacy, the above efficacy analysis is considered descriptive. However, this analysis is included in labeling and does provide reasonable evidence for the efficacy of the Original Monovalent vaccine.

Primary Immunogenicity Endpoints:

The adjusted ratio of geometric mean and difference in seroconversion rate of MN Assay Neutralizing Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35 for the primary 2-dose series in the PP-IMM population (Adult Main Study (18 to <26 Years) Vs Pediatric Expansion (12 to <18 Years)) is presented in the table below.

Table 67. Adjusted Ratio of Geometric Mean and Difference in Seroconversion Rate of MN Assay Neutralizing Antibody Titers for SARS-CoV-2 S Wild-Type Virus at Day 35, PP-IMM Analysis Set, Pediatric Expansion Study 301

Parameter	Adult Main Study (18 to <26 Years) N=416	Pediatric Expansion (12 to <18 Years) N=390	Parameter	Adult Main Study (18 to <26 Years) Vs Pediatric Expansion (12 to <18 Years) Met NI Criteria (Yes/No)
Day 35	--	--	--	--
n	416	390	n1*, n2*	416, 390
GMT[a]	2633.6	3859.6	GMR[b]	0.7 Yes
95% CI[b]	(2388.6, 2903.6)	(3422.8, 4352.1)	95% CI	(0.6, 0.8) Yes
Day 35 seroconversion	--	--	--	--
n3	415	385	--	--
SCR[c]	99.8	98.7	Difference	1.1
95% CI[c]	(98.7, 100.0)	(97.0, 99.6)	95% CI[d]	(-0.2, 2.8) Yes

Source: Study 301 12-month Adolescent CSR, page 140, Table 53
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMR=ratio of GMT, which is defined as the ratio of 2 GMTs for comparison of 2 age cohorts; GMT=geometric mean titer; LLOQ=lower limit of quantitation; MN=microneutralization; N=number of participants in assay-specific PP-IMM Analysis Set in each part of study; n=number of participants with non-missing response at each visit; n1*=number of participants in adult part of study (18 to <26 years) with non-missing neutralizing antibodies result at both Day 0 and Day 35; n3=number of participants who reported a ≥4- fold increase; NI=noninferiority; PP-IMM=Per-Protocol Immunogenicity; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=seroconversion rate
a. The 95% CI for GMT was calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
b. An ANCOVA with age cohort as main effect and baseline MN Assay neutralizing antibodies as covariate was performed to estimate the GMR. Individual response values recorded as below the LLOQ were set to half LLOQ.
c. SCR is defined as percentage of participants with a ≥4-fold difference in titers between Day 35 and Day 0. The 95% CI for SCR was calculated using the Clopper-Pearson exact method.
d. Difference in SCR in the adult part of the study for participants 18 to <26 years of age minus SCR in the pediatric expansion. The 95% CI for the difference of SCR between groups was calculated with the method of Miettinen and Nurminen.
Note: table includes participants in the active vaccine group only.
e. Noninferiority of the single booster dose was achieved if the lower limit of the 95% CI for the ratio of MN50 GMT at 28 days after a single booster dose versus 14 days after the second dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was >0.67 and point estimate >0.83.
f. Noninferiority of the single booster dose was achieved if the lower limit of the 95% CI for the difference of the percentage of participants with SCR at 28 days after a single booster dose relative to the time of first vaccination versus at 14 days after the second dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) relative to the time of first vaccination was >-10%.

Reviewer Comment: Immunogenicity analyses for prespecified co-primary immunogenicity endpoints (GMR and SCR difference) met noninferiority criteria, which in the context of the descriptive efficacy data discussed above, provides evidence for inferring vaccine effectiveness of the 2-dose primary series of the Original Wuhan vaccine in adolescents 12 through 17 years of age.

The neutralizing antibody geometric titers (MN_{50}) and seroconversion rates against the original SARS-CoV-2 virus strain at 28 days after a booster dose versus 14 days after completion of the primary series in participants 12 through 17 years of age, for the PP-IMM Analysis Set is presented in the table below.

Table 68. Neutralizing Antibody Geometric Titers (MN_{50}) and Seroconversion Rates Against the Original SARS-CoV-2 Virus Strain at 28 Days After a Booster Dose Versus 14 Days After Completion of the Primary Series in Participants 12 Through 17 Years of Age, PP-IMM Analysis Set[a], Pediatric Expansion Study 301

Parameter	28 Days After Booster Dose n=56[b]	14 Days After Primary Series Dose 2 n=56[b]	Comparison	Met Noninferiority Criteria[g,h]
GMT (95% CI)[c]	12177.5 (9294.6, 15954.6)	4305.4 (3543.7, 5230.7)	GMR (95% CI)[c] 2.8 (2.1, 3.8)	Yes
SCR% (95% CI)[d]	100.0 (93.6, 100.0)	100.0 (93.6, 100.0)	Difference in SCR%[e] (95% CI)[f] 0.0 (-6.4, 6.4)	Yes

Source: Adapted from 2019nCoV-301 12-Month Adolescent Clinical Study Report, dated July 21, 2023, submitted to STN 125817/0/4, Table 60, p. 153.
Abbreviations: CI=confidence interval; GMR=geometric mean ratio; GMT=geometric mean titer; LLOQ=lower limit of quantitation; MN50=microneutralization assay with an inhibitory concentration of 50%; PP-IMM=Per-Protocol Immunogenicity; SCR=seroconversion rate; n=number of participants in PP-IMM analysis subset (see footnote b)
a. The PP-IMM Analysis Set included participants who received two doses (0.5 mL 21 days apart) of Nuvaxovid in the initial vaccination period , had an immunogenicity blood sample collected at Day 35 (primary series) and at 28 days after booster dose vaccination, did not have serologic or virologic evidence of SARS-CoV-2 infection on or before the booster dose, did not receive an emergency use authorized COVID-19 vaccine, received the booster dose, and remained blinded on study and without major protocol deviations until 7 days post-crossover Dose.
b. The analysis included a total of 56 participants of the PP-IMM analysis set who had immunogenicity data available for both the booster dose and primary series.
c. The 95% CI for GMT and GMT ratio were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
d. The 95% CI for SCR was based on the Clopper-Pearson method.
e. The difference in SCR was based on the Tango method.
f. Comparison between SCR of 28 days post-booster dose relative to time of first dose and SCR of 14 days after second dose of the primary series relative to time of first dose.
g. Noninferiority of the single booster dose was achieved if the lower limit of the 95% CI for the ratio of MN50 GMT at 28 days after a single booster dose versus 14 days after the second dose of Nuvaxovid was >0.67 and point estimate >0.83.
h. Noninferiority of the single booster dose was achieved if the lower limit of the 95% CI for the difference of the proportion of participants with SCR at 28 days after a single booster dose relative to the time of first vaccination versus at 14 days after the second dose of Nuvaxovid relative to the time of first vaccination was >-10%.
Note: The median duration between the time of the second dose of Nuvaxovid, and the time of the booster dose was 10.6 months.
Note: SCR was defined as percentage of participants with a ≥4-fold rise from baseline if the baseline value is equal to or above LLOQ, or at least 4-fold rise from LLOQ if the baseline value is below LLOQ in antibody concentration.

Reviewer Comment: This immunogenicity analysis met noninferiority criteria for GMR and SCR difference which in the context of the descriptive efficacy data discussed above, provides evidence for inferring vaccine effectiveness for a third vaccine dose of the Original Wuhan vaccine in adolescents 12 through 17 years of age.

6.2.11.2 Analyses of Secondary Endpoints

Through the observation period covered by this analysis, the circulation of variant strains evolved in the U.S. such that the predominantly circulating strains became largely those known as VOC or VBM according to CDC SARS-CoV-2 Variant Classifications and Definitions for December 2021. Since Original Monovalent contains the recombinant S protein produced from the original prototype (Wuhan) genome, VE against “ancestral-like” strains (those not considered as a VOC, VOI [variant of interest], or VBM) was a secondary endpoint of the study. There were no cases due to a SARS-CoV-2 variant not considered as a VOC or VBM in the Pediatric Expansion during this period. Therefore, this endpoint could not be estimated.

In the PP-EFF Analysis Set, 11 cases [3 (0.3%) in the Original Monovalent and 8 (1.4%) in the placebo group] had mutations that would identify them as VOC/VBM. In Original Monovalent and placebo group, all cases were mild in severity. The resultant VE of Original Monovalent to

prevent symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered a VOC or VBM in baseline seronegative participants was 82.3% (95% CI: 33.5, 95.3); see table below.

Table 69. Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 Due to a SARS-CoV-2 Variant Considered as a VOC/VBM (March 2022 CDC Classification) With Onset From at Least 7 Days After Second Vaccination of the Crossover Vaccination Period in Baseline Serologically Negative/PCR-Negative Adolescent Participants, PP-EFF Analysis Set, Pediatric Expansion Study 301

Parameter	Original Monovalent N=1199	Placebo N=589
Participants with no occurrence of case[a], n (%)	1196 (99.7)	581 (98.6)
Participants with occurrence of case[b], n (%)	3 (0.3)	8 (1.4)
Severity of first occurrence, n (%)	--	--
Mild	3 (0.3)	8 (1.4)
Moderate	0	0
Severe	0	0
Median surveillance time[c] (days)	64.0	63.0
Log-linear model using modified Poisson regression[d]	--	--
Mean Disease Incidence Rate (/100-person year)	1.4	8.2
95% CI	0.5, 4.5	4.1, 16.3
Relative risk	0.2	--
95% CI	0.1,0.7	--
Vaccine efficacy (%)	82.3	--
95% CI	33.6, 95.3	--

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR Table 11, page 34
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction; PP-EFF=Per-Protocol Efficacy; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; VE=vaccine efficacy; VOC=Variants of Concern; VOI=Variants of Interest; N=The PP-EFF analysis set, which included all participants who received the full regimen of trial vaccine and had no major protocol deviations that occurred before the first COVID-19 positive episode (i.e., participant was censored at the time of the protocol deviation) and that were determined to affect the efficacy outcomes, including baseline SARS-CoV-2 seropositivity or nasal swab PCR-positivity; n=number of unique participants per category.
a. Includes participants with PCR-confirmed infection who did not meet mild, moderate, or severe COVID-19 criteria and not considered a VOC or VOI.
b. Case=first occurrence of PCR-confirmed mild, moderate, or severe COVID-19 due to a VOC or VBM with onset of illness episode from at least 7 days after second vaccination within the surveillance period.
c. Surveillance time was defined as the difference between the date at end of surveillance period (onset of first occurrence of case/censoring) and date at start of surveillance period (7 days after the Second Injection) +1.
d. Modified Poisson regression with logarithmic link function, treatment group as fixed effects and robust error variance [Zou 2004].
Note: VOC/VBM were established by SIG and CDC for SARS-CoV-2 Variant Classifications and Definitions for March 2022

6.2.11.3 Subpopulation Analyses

Subgroup analysis of additional demographic and baseline characteristics resulted in VEs consistent with that reported for the primary efficacy endpoint (i.e., 79.8% [95% CI: 47.5, 92.2]), see table below.

Table 70. Subgroup Analyses of the Vaccine Efficacy Against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 With Onset from at Least 7 Days After Second Vaccination of the Crossover Vaccination Period in Baseline Serologically Negative/PCR-Negative Adolescent Participants, PP-EFF Analysis Set, Pediatric Expansion Study 301

Characteristic	Original Monovalent Cases[a]/N (%) (Mean Disease Incidence Rate/100 Person-Years)[b]	Placebo Cases[a]/N (%) (Mean Disease Incidence Rate/100 Person-Years)[b]	Vaccine Efficacy, % (95% CI)
Age	--	--	--
12 to <15 years old	4/818 (0.5)	10/404 (2.5)	80.9 (39.2, 94.0)
15 to <18 years old	2/381 (0.5)	4/185 (2.2)	77.2 (-24.2, 95.8)
Sex	--	--	--
Male	3/618 (0.5)	4/324 (1.2)	62.8 (-66.1, 91.7)
Female	3/581 (0.5)	10/265 (3.8)	86.7 (51.8, 96.3)
Race (summary)	--	--	--
White	6/920 (0.7)	13/445 (2.9)	78.9 (44.5, 92.0)
Non-White	0/272	1/141 (0.7)	100.0 (-1904.2, 100.0)
Race (individual)	--	--	--
White	6/920 (0.7)	13/444 (2.9)	78.9 (44.5, 92.00)
Black or African American	0/153	0/77	N/A
American Indian or Alaska Native	0/13	0/6	N/A
Asian	0/37	0/24	N/A
Native Hawaiian or Other Pacific Islander	0/3	0/1	N/A
Mixed Origin	0/66	1/33 (3.0)	100.0 (-1915.7,100.0)
Ethnicity	--	--	--
Hispanic or Latino	0/187	1/100 (1.0)	100.0 (-1917.0, 100.0)
Not Hispanic or Latino	6/1007 (0.6)	13/489 (2.7)	78.6 (43.7, 91.8)
BMI	--	--	--
Obese	**2/313 (0.6)**	**2/139 (1.4)**	**56.3 (-503.2, 96.8)**
Non-obese	**4/886 (0.5)**	**12/450 (2.7)**	**83.9 (50.1, 94.8)**

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR Table 9, page 30
Abbreviations: BMI=body mass index; CI=confidence interval; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; NE=not estimable in the event the test for exact binomial proportion cannot be conducted; NP=nucleocapsid protein; PCR=polymerase chain reaction; RR=relative risk; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; U.S.=United States; VE=vaccine efficacy.
a. Case=First occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second injection within the surveillance period.
b. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adolescents who received both doses of trial vaccine (Original Monovalent or placebo) in the initial vaccination period. RR was the ratio of incidence rates of active group relative to the placebo group (NVX- CoV2373/placebo) with first occurrence of case with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cutoff date (06 August 2022), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended receipt of alternative COVID-19 vaccine), (v) end of follow-up, (vi) first dose of blinded crossover, or (vii) first booster dose. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 criteria were censored at date of the PCR-positive.
c. In case when there were zero cases in either treatment group or the total number of cases in both treatment groups combined <5, VE and 95% CI was calculated using the Clopper-Pearson exact binomial method that conditions on the total number of cases and was adjusted for total surveillance time.
Note: RR based on log-linear model of occurrence using modified Poisson regression with logarithmic link function, treatment group as fixed effects and robust error variance [Zou 2004] fitted separately to each subgroup.

Reviewer Comment: Vaccine efficacy was slightly lower in males (62.8% (95% CI: -66.1, 91.7) compared with females (86.7% (95% CI: 51.8, 96.3)) and obese participants (56.3% (95% CI: -503.2, 96.8)) compared with nonobese participants (83.9% (95% CI: 50.1, 94.8)), but these results are inconclusive due to underpowering.

6.2.11.4 Dropouts and/or Discontinuations

The number of participants who dropped out and/or discontinued from the study did not affect the interpretation of the vaccine efficacy outcomes. Refer to Section 6.2.12.7 for details regarding dropouts and/or discontinuations.

6.2.12 Safety Analyses

6.2.12.1 Methods

Please see section 6.1.12.1.

6.2.12.2 Overview of Adverse Events

Duration of Safety Follow-up

For the pre-crossover vaccination period, median follow-up after the second dose was 71 days with 86.2% of participants in the NVX-CoV2373 (Original monovalent) group and 83.8% of participants in the placebo group being followed for at least 2 months after the second dose. For the post-crossover vaccination period, median follow-up after the second dose was 234 days with 99.7% of participants in the Original monovalent group and 99.8% of participants in the placebo group being followed for at least 2 months after the second dose. For the booster vaccination period, median follow up after the second crossover dose was 3.4 months with approximately 97.9% of participants being followed for at least 2 months after the booster dose.

Solicited Local Adverse Events

The following table presents a summary of solicited local injection site adverse reactions (ARs) at participants in the Safety Analysis Set experienced within 7 days after each dose of the 2-dose series compared with placebo.

Table 71. Characteristics of Solicited Local Injection Site TEAEs Within 7 Days After Each Dose, Safety Analysis Set, Pediatric Expansion Study 301

Event	Original Monovalent Dose 1 N=1448	Placebo Dose 1 N=726	Original Monovalent Dose 2 N=1394	Placebo Dose 2 N=686
Any solicited local TEAE	--	--	--	--
n	948	207	1050	141
Day of onset: median (min, max)	1 (1, 7)	1 (1, 7)	1 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	3 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	5	0	1	0
Pain/Tenderness	--	--	--	--
n	945	204	1045	141
Day of onset: median (min, max)	1 (1, 7)	1 (1, 7)	1 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	3 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	5	0	1	0
Pain	--	--	--	--
n	647	126	850	102
Day of onset: median (min, max)	1 (1, 7)	1 (1, 6)	2 (1, 7)	1 (1, 7)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	2 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	3	0	1	0

Event	Original Monovalent Dose 1 N=1448	Placebo Dose 1 N=726	Original Monovalent Dose 2 N=1394	Placebo Dose 2 N=686
Tenderness	--	--	--	--
n	819	153	909	97
Day of onset: median (min, max)	2 (1, 7)	1 (1, 7)	2 (1, 7)	1 (1, 5)
Duration within period: median (min, max)	2 (1, 7)	1 (1, 7)	2 (1, 7)	1 (1, 7)
Persisted beyond 7 days[a]	3	0	1	0
Redness	--	--	--	--
n	15	5	104	0
Day of onset: median (min, max)	2 (1, 7)	1 (1, 2)	2 (1, 5)	0
Duration within period: median (min, max)	2 (1, 6)	1 (1, 1)	2 (1, 6)	0
Persisted beyond 7 days[a]	0	0	0	0
Swelling	--	--	--	--
n	20	3	111	1
Day of onset: median (min, max)	2 (1, 3)	2 (2, 3)	2 (1, 5)	2 (2, 2)
Duration within period: median (min, max)	1 (1, 6)	2 (1, 3)	2 (1, 6)	1 (1, 1)
Persisted beyond 7 days[a]	0	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 17, 43-44
Abbreviations: COVID=coronavirus disease 2019; max=maximum; min=minimum; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of post dose reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
a. Events reported on the Adverse Events CRF indicated as continuing from the Diary Card for solicited local and/or systemic events and coded to a term matching a solicited reactogenicity term.
Solicited local injection site ARs were reported most frequently among Original Monovalent recipients than among placebo recipients after each dose of the 2-dose series. Overall, solicited local ARs had an onset on Day 1 of the study and had median durations of 2 days for Dose 1 and 3 days for Dose 2, which were longer than the 1-day median duration of adverse reactions for placebo recipients. Among Original Monovalent recipients, there were 2 participants with delayed local injection site ARs: 1 participant with injection site pruritis (onset on Day 7 of the study and duration of 4 days) and 1 with injection site pain and swelling (onset on Day 7 of the study and duration of 2-3 days). For recipients of the Original Monovalent vaccine, reports of all solicited local ARs (pain, tenderness, redness, swelling) increased from Dose 1 to Dose 2 of study vaccine.

Table 72. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Each Dose, Safety Analysis Set, Pediatric Expansion Study 301

Event	Original Monovalent Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Any solicited local injection site TEAEs	--	--	--	--
Any (Grade ≥1)	948 (65.5)	207 (28.5)	1050 (75.3)	141 (20.6)
Grade 3	22 (1.5)	4 (0.6)	118 (8.5)	4 (0.6)
Grade 4	0	0	0	0
Pain/Tenderness	--	--	--	--
Any (Grade ≥1)	945 (65.3)	204 (28.1)	1045 (75.0)	141 (20.6)
Grade 3	22 (1.5)	4 (0.6)	108 (7.7)	4 (0.6)
Grade 4	0	0	0	0
Pain	--	--	--	--
Any (Grade ≥1)	647 (44.7)	126 (17.4)	850 (61.0)	102 (14.9)
Grade 3	10 (0.7)	2 (0.3)	38 (2.7)	3 (0.4)
Grade 4	0	0	0	0

Event	Original Monovalent Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Any solicited local injection site TEAEs	--	--	--	--
Tenderness	--	--	--	--
Any (Grade ≥1)	819 (56.6)	153 (21.1)	909 (65.2)	97 (14.1)
Grade 3	16 (1.1)	2 (0.3)	93 (6.7)	1 (0.1)
Grade 4	0	0	0	0
Redness	--	--	--	--
Any (Grade ≥1)	15 (1.0)	5 (0.7)	104 (7.5)	0
Grade 3	0	0	10 (0.7)	0
Grade 4	0	0	0	0
Swelling	--	--	--	--
Any (Grade ≥1)	20 (1.4)	3 (0.4)	111 (8.0)	1 (0.1)
Grade 3	0	0	8 (0.6)	0
Grade 4	0	0	0	0

Source: 2019nCoV-301: 12-Month Adolescent Report, Table 70, 175-176
Abbreviations: TEAE=treatment emergent adverse event
Events reported on the Adverse Events CRF indicated as continuing from the Diary Card for solicited local and/or systemic events and coded to a term matching a solicited reactogenicity term. Column header counts and denominators were the number of participants in the Safety Analysis Set within each treatment arm who received the dose of interest and completed at least one day of the post-dose reactogenicity diary.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The table below shows that within the 7 days following each dose of Original Monovalent 2-dose series, solicited local injection site ARs were reported more frequently by Original Monovalent recipients than placebo recipients for both Dose 1 (65% versus 28.5%, respectively) and Dose 2 (75.3% versus 20.6%, respectively). Pain and/or tenderness were the most frequently reported solicited local injection site ARs reported after each vaccination. Unlike placebo recipients in which reports of adverse reactions generally decreased from Dose 1 to Dose 2, the percentage of participants reporting ARs increased from Dose 1 to Dose 2 of Original Monovalent recipients for every adverse reaction. Notably, the percentage of participants reporting Grade 3 solicited local injection site reactions increased with each consecutive dose from 1.5% to 8.5% of participants for Dose 1 and Dose 2, respectively. There were no Grade 4 solicited local adverse reactions. The following table presents the percentages of participants in the Safety Analysis Set who reported solicited local injection site ARs within 7 days after each dose of the 2-dose series and the 3rd dose (booster).

Table 73. Frequency and Percentage of Solicited Local Injection Site TEAEs Within 7 Days After Primary, Safety Analysis Set, and Booster, Booster Safety Analysis Set, Vaccination With Original Monovalent in Adolescent Participants, Pediatric Expansion Study 301

Event	Original Monovalent Dose 1 N=1448 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Total Boosted Dose 3 N=1256 n (%)
Any solicited local injection site TEAE	--	--	--
Any (Grade ≥1)	948 (65.5)	1050 (75.3)	969 (77.1)
Grade 3	22 (1.5)	118 (8.5)	167 (13.3)
Grade 4	0	0	1 (<0.1)

Event	Original Monovalent Dose 1 N=1448 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Total Boosted Dose 3 N=1256 n (%)
Pain/tenderness	--	--	--
Any (Grade ≥1)	945 (65.3)	1045 (75.0)	964 (76.8)
Grade 3	22 (1.5)	108 (7.7)	145 (11.5)
Grade 4	0	0	1 (<0.1)
Pain	--	--	--
Any (Grade ≥1)	647 (44.7)	850 (61.0)	812 (64.6)
Grade 3	10 (0.7)	38 (2.7)	61 (4.9)
Grade 4	0	0	0
Tenderness	--	--	--
Any (Grade ≥1)	819 (56.6)	909 (65.2)	828 (65.9)
Grade 3	16 (1.1)	93 (6.7)	116 (9.2)
Grade 4	0	0	1 (<0.1)
Redness	--	--	--
Any (Grade ≥1)	15 (1.0)	104 (7.5)	129 (10.3)
Grade 3	0	10 (0.7)	29 (2.3)
Grade 4	0	0	0
Swelling	--	--	--
Any (Grade ≥1)	20 (1.4)	111 (8.0)	119 (9.5)
Grade 3	0	8 (0.6)	18 (1.4)
Grade 4	0	0	0

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 18, Page 45-46
Abbreviations: COVID=coronavirus disease 2019; FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the vaccination reactogenicity diary reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
Events reported on the Adverse Events CRF indicated as continuing from the Diary Card for solicited local and/or systemic events and coded to a term matching a solicited reactogenicity term. Column header counts and denominators were the number of participants in the Safety Analysis Set within each treatment arm who received the dose of interest and completed at least one day of the post-dose reactogenicity diary.
Note: All percentages are based on n/N*100.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

The table below shows that within the 7 days following the 3rd dose of Original Monovalent, solicited local injection site ARs were most frequently reported on Day 2 and on Day 3 postvaccination. The median duration of local injection site ARs following the 3rd dose was 3 days. Solicited local injection site TEAEs that persisted beyond 7 days were infrequent.

Solicited local injection site ARs within 7 days after the 3rd dose of Original Monovalent vaccine were reported by 77.1% of adolescent participants in the booster period. Most solicited local ARs were Grade 1 or Grade 2 in intensity, with Grade 3 events reported for 13.3% of participants and Grade 4 events reported for 1 (<0.1%) participant. Pain and/or tenderness were the most frequently reported solicited local injection site ARs after the 3rd vaccine dose.

Following administration of any dose of Original Monovalent vaccine, most ARs were Grade 1 or 2 in intensity. Notably, the percentage of participants reporting Grade 3 solicited local injection site reactions increased with each consecutive dose for 1.5%, 8.5%, and 13.3% of participants for Dose 1, 2, and 3, respectively. The frequency of Grade 4 events remained the same for Dose 1 and Dose 2 and increased to <0.1% with the 3rd dose.

Subgroup analyses were conducted for solicited local adverse reactions within 7 days after Dose 1 and Dose 2 of the initial 2-dose series and the frequency and percentage are presented in the table below.

Table 74. Frequency and Percentage, by Subgroup, of Solicited Local Adverse Events Within 7 Days After Dose 1 and Dose 2 by Demographic and Baseline Characteristics, Safety Analysis Set, Pediatric Expansion Study 301

Subgroup	Original Monovalent Any Grade n/N (%)	Original Monovalent ≥Grade 3 n/N (%)	Placebo Any Grade n/N (%)	Placebo ≥Grade 3 n/N (%)
All participants	--	--	--	--
Dose 1	948/1448 (65.5)	22/1448 (1.5)	207/726 (28.5)	4/726 (0.6)
Dose 2	1050/1394 (75.3)	118/1394 (8.5)	141/686 (20.6)	4/686 (0.6)
Age	--	--	--	--
Participants 12 to <15 years	--	--	--	--
Dose 1	638/970 (65.8)	16/970 (1.6)	152/487 (31.2)	2/487 (0.4)
Dose 2	708/935 (75.7)	79/935 (8.4)	108/461 (23.4)	3/461 (0.7)
Participants 15 to <18 years	--	--	--	--
Dose 1	310/478 (64.9)	6/478 (1.3)	55/239 (23.0)	2/239 (0.8)
Dose 2	342/459 (74.5)	39/459 (8.5)	33/225 (14.7)	1/225 (0.4)
Sex	--	--	--	--
Male	--	--	--	--
Dose 1[a]	427/744 (57.4)	5/744 (0.7)	102/405 (25.2)	1/405 (0.2)
Dose 2	484/702 (68.9)	51/702 (7.3)	58/386 (15.0)	2/386 (0.5)
Female	--	--	--	--
Dose 1[a]	521/704 (74.0)	17/~~321~~ 704 (2.4)	105/321 (32.7)	3/321 (0.9)
Dose 2	566/692 (81.8)	67/692 (9.7)	83/300 (27.7)	2/300 (0.7)
Race	--	--	--	--
White	--	--	--	--
Dose 1	753/1093 (68.9)	15/1093 (1.4)	157/535 (29.3)	2/535 (0.4)
Dose 2	838/1057 (79.3)	96/1057 (9.1)	108/510 (21.2)	1/510 (0.2)
Black or African American	--	--	--	--
Dose 1	95/189 (50.3)	1/189 (0.5)	25/100 (25.0)	0/100 (0.0)
Dose 2	102/180 (56.7)	8/180 (4.4)	17/90 (18.9)	2/90 (2.2)
Asian	--	--	--	--
Dose 1	24/42 (57.1)	0/42 (0.0)	8/34 (23.5)	0/34 (0.0)
Dose 2	31/41 (75.6)	2/41 (4.9)	5/31 (16.1)	0/31 (0.0)
American Indian or Alaska Native	--	--	--	--
Dose 1	11/30 (36.7)	2/30 (6.7)	3/14 (21.4)	1/14 (7.1)
Dose 2	13/29 (44.8)	2/29 (6.9)	3/13 (23.1)	0/13 (0.0)
Native Hawaiian or other Pacific Islander	--	--	--	--
Dose 1	2/3 (66.7)	0/3 (0.0)	2/2 (100)	0/2 (0.0)
Dose 2	3/3 (100)	0/3 (0.0)	1/2 (50.0)	0/2 (0.0)
Mixed origin	--	--	--	--
Dose 1	55/81 (67.9)	1/81 (1.2)	11/36 (30.6)	1/36 (2.8)
Dose 2	56/76 (73.7)	7/76 (9.2)	6/35 (17.1)	1/35 (2.9)
Not reported	--	--	--	--
Dose 1	8/10 (80.0)	3/10 (30.0)	1/5 (20.0)	0/5 (0.0)
Dose 2	7/8 (87.5)	3/8 (37.5)	1/5 (20.0)	0/5 (20.0)

Subgroup	Original Monovalent Any Grade n/N (%)	Original Monovalent ≥Grade 3 n/N (%)	Placebo Any Grade n/N (%)	Placebo ≥Grade 3 n/N (%)
Ethnicity	--	--	--	--
Not Hispanic or Latino	--	--	--	--
Dose 1	785/1174 (66.9)	16/1174 (1.4)	174/591 (29.4)	2/591 (0.3)
Dose 2	875/1136 (77.0)	94/1136 (8.3)	118/558 (21.1)	4/558 (0.7)
Hispanic or Latino	--	--	--	--
Dose 1	159/269 (59.1)	6/269 (2.2)	33/135 (24.4)	2/135 (1.5)
Dose 2	171/253 (67.6)	24/253 (9.5)	23/128 (18.0)	0/128 (0.0)
Not reported	--	--	--	--
Dose 1	2/2 (100.0)	0/2 (0.0)	0/0 (0.0)	0/0 (0.0)
Dose 2	2/2 (100.0)	0/2 (0.0)	0/0 (0.0)	0/0 (0.0)

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 25, Page 57-59
Abbreviations: COVID=coronavirus disease 2019; FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
a. Original numbers for this category were incorrectly applied from the source table.
Note: Data were presented as number (%) of participants experiencing a solicited event. Percentages were based on n/N1 × 100 and n/N2 × 100. At each level of participant summarization, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period was summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

Solicited Systemic Adverse Events

By subgroup analyses,

- Solicited local ARs reported by Original Monovalent recipients after each vaccination were balanced across age subgroup (12 to <15 years and 15 to <18 years). For the placebo group, there was increased reporting of solicited local ARs in the younger age subgroup (12 to <15 years).
- Male participants reported lower frequencies and intensities of solicited local ARs among both Original Monovalent and placebo as compared with the female participants.
- Black or African American and American Indian or Alaska Native participants reported lower frequencies and severities of solicited local ARs among Original Monovalent recipients after each vaccination than in participants of other races.
- Hispanic or Latino participants reported lower frequencies of solicited local ARs among both Original Monovalent and placebo recipients after each vaccination than in not Hispanic or Latino participants. Severity (based on percentage of participants with grade 3+ local ARs), however, was similar among the 2 ethnic groups.

Clinical Reviewer Comment: The reactogenicity of the Original monovalent vaccine appears to increase with each consecutive dose, as evidenced by increasing reports of solicited local ARs and Grade 3 reactions with each dose. Tenderness and pain were the most frequent solicited local adverse reactions across the initial 2-dose series and booster vaccination periods. In general, subgroups analyzed by age, sex, race, and ethnicity demonstrated similar trends in local reactogenicity.

The following table presents solicited systemic adverse reactions reported by participants in the Safety Analysis Set within 7 days after each dose in the initial 2-dose series.

Table 75. Frequency and Percentage of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set, Pediatric Expansion Study 301

Event	Original Monovalent Dose 1 N=1448 n (%)	Placebo Dose 1 N=726 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Placebo Dose 2 N=686 n (%)
Any solicited systemic reaction	--	--	--	--
Any (Grade ≥1)	799 (55.2)	296 (40.8)	1038 (74.5)	198 (28.9)
Grade 3	52 (3.6)	25 (3.4)	305 (21.9)	23 (3.4)
Grade 4	0	0	2 (0.1)	0
Fever	--	--	--	--
Any (Grade ≥1)	9 (0.6)	4 (0.6)	235 (16.9)	1 (0.1)
Grade 3	1 (<0.1)	0	31 (2.2)	0
Grade 4	0	0	0	0
Headache	--	--	--	--
Any (Grade ≥1)	440 (30.4)	181 (24.9)	793 (56.9)	119 (17.3)
Grade 3	13 (0.9)	12 (1.7)	87 (6.2)	14 (2.0)
Grade 4	0	0	1 (<0.1)	0
Fatigue/malaise	--	--	--	--
Any (Grade ≥1)	418 (28.9)	142 (19.6)	807 (57.9)	113 (16.5)
Grade 3	33 (2.3)	13 (1.8)	225 (16.1)	14 (2.0)
Grade 4	0	0	0	0
Fatigue	--	--	--	--
Any (Grade ≥1)	350 (24.2)	112 (15.4)	696 (49.9)	100 (14.6)
Grade 3	23 (1.6)	9 (1.2)	189 (13.6)	11 (1.6)
Grade 4	0	0	0	0
Malaise	--	--	--	--
Any (Grade ≥1)	215 (14.8)	67 (9.2)	560 (40.2)	51 (7.4)
Grade 3	16 (1.1)	7 (1.0)	126 (9.0)	4 (0.6)
Grade 4	0	0	0	0
Muscle pain (myalgia)	--	--	--	--
Any (Grade ≥1)	492 (34.0)	114 (15.7)	684 (49.1)	82 (12.0)
Grade 3	17 (1.2)	4 (0.6)	104 (7.5)	6 (0.9)
Grade 4	0	0	0	0
Joint pain (arthralgia)	--	--	--	--
Any (Grade ≥1)	102 (7.0)	35 (4.8)	225 (16.1)	21 (3.1)
Grade 3	6 (0.4)	1 (0.1)	40 (2.9)	2 (0.3)
Grade 4	0	0	0	0
Nausea/vomiting	--	--	--	--
Any (Grade ≥1)	113 (7.8)	56 (7.7)	277 (19.9)	33 (4.8)
Grade 3	2 (0.1)	3 (0.4)	14 (1.0)	3 (0.4)
Grade 4	0	0	1 (<0.1)	0

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 26, Page 60-61
Abbreviations: COVID=coronavirus disease 2019; FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) dose and completed at least one day of the reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
Note: At each level of summarization, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period was summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

Solicited systemic adverse reactions were reported at higher percentages among Original Monovalent recipients than among placebo recipients after each vaccination, and at higher

intensities after the second vaccination. Most solicited systemic reactions were Grade 1 or Grade 2 in intensity. However, Grade 3 or higher solicited systemic reactions were reported by 21.9% of Original Monovalent recipients; 2 participants reported Grade 4 events after receiving the second dose.

Following the second dose, an increase in percentage and intensity in solicited systemic reactions relative to the first dose was observed in the Original Monovalent group (55.2% vs 74.5%).

Solicited systemic ARs within 7 days after the booster dose of Original Monovalent were reported by 80.8% of adolescent participants, with the majority of events being Grade 1 or Grade 2 in severity (see table below). Grade 3 solicited systemic TEAEs were reported for 29.9% participants and Grade 4 events were reported for 5 (0.4%) participants following the booster dose. Fatigue/malaise and headache were the most frequently reported systemic events. Fatigue/ Malaise was the most frequent Grade ≥3 solicited systemic TEAE (21.4%).

Following administration of Original Monovalent, the percentage of solicited systemic TEAEs of any grade (Grade ≥1) increased from Dose 1 to Dose 2 during the primary series but increased to a higher degree for Dose 2 and the booster dose (see table below). Although most events reported following any dose of Original Monovalent were Grade 1 or 2 in intensity, the percentage of Grade 3 solicited systemic TEAEs increased with each consecutive dose, with 3.6%, 21.9%, and 29.9% participants, reporting Grade 3 events for Dose 1, Dose 2, and the booster dose, respectively.

There were no Grade 4 events reported for Dose 1 and increased 0.1% in Dose 2 and further increased 0.4% in the booster dose. Fatigue/Malaise were the most frequent Grade ≥3 solicited systemic TEAE across the primary and booster vaccination periods.

Table 76. Frequency and Percentage of Solicited Systemic TEAEs Within 7 Days After Primary, Safety Analysis Set, and Booster, Booster Safety Analysis Set, Vaccination of Original Monovalent in Adolescent, Pediatric Expansion Study 301

Event	Original Monovalent Dose 1 N=1448 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Total Boosted Dose 3 N=1256 n (%)
Any solicited systemic reaction	--	--	--
Any (Grade ≥1)	799 (55.2)	1038 (74.5)	1015 (80.8)
Grade 3	52 (3.6)	305 (21.9)	375 (29.9)
Grade 4	0	2 (0.1)	5 (0.4)
Fever	--	--	--
Any (Grade ≥1)	9 (0.6)	235 (16.9)	211 (16.8)
Grade 3	1 (<0.1)	31 (2.2)	44 (3.5)
Grade 4	0	0	3 (0.2)
Headache	--	--	--
Any (Grade ≥1)	440 (30.4)	793 (56.9)	790 (62.9)
Grade 3	13 (0.9)	87 (6.2)	154 (12.3)
Grade 4	0	1 (<0.1)	2 (0.2)
Fatigue/malaise	--	--	--
Any (Grade ≥1)	418 (28.9)	807 (57.9)	791 (63.0)
Grade 3	33 (2.3)	225 (16.1)	269 (21.4)
Grade 4	0	0	1 (<0.1)

Event	Original Monovalent Dose 1 N=1448 n (%)	Original Monovalent Dose 2 N=1394 n (%)	Total Boosted Dose 3 N=1256 n (%)
Fatigue	--	--	--
Any (Grade ≥1)	350 (24.2)	696 (49.9)	717 (57.1)
Grade 3	23 (1.6)	189 (13.6)	216 (17.2)
Grade 4	0	0	1 (<0.1)
Malaise	--	--	--
Any (Grade ≥1)	215 (14.8)	560 (40.2)	566 (45.1)
Grade 3	16 (1.1)	126 (9.0)	170 (13.5)
Grade 4	0	0	1 (<0.1)
Muscle pain (myalgia)	--	--	--
Any (Grade ≥1)	492 (34.0)	684 (49.1)	758 (60.4)
Grade 3	17 (1.2)	104 (7.5)	143 (11.4)
Grade 4	0	0	1 (<0.1)
Joint pain (arthralgia)	--	--	--
Any (Grade ≥1)	102 (7.0)	225 (16.1)	275 (21.9)
Grade 3	6 (0.4)	40 (2.9)	50 (4.0)
Grade 4	0	0	1 (<0.1)
Nausea/vomiting	--	--	--
Any (Grade ≥1)	113 (7.8)	277 (19.9)	296 (23.6)
Grade 3	2 (0.1)	14 (1.0)	20 (1.6)
Grade 4	0	1 (<0.1)	0

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 29 page 67
Abbreviations: COVID=coronavirus disease 2019; FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the first dose (Dose 1) and second dose (Dose 2) and completed at least one day of the reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
Note: At each level of summarization, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period was summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

Across all demographic and baseline characteristic subgroups, there were higher percentages of solicited systemic TEAEs among Original Monovalent recipients than among placebo recipients following each vaccination (see table below).

- Male participants reported lower percentages and intensities of solicited systemic reactions than female participants among both Original Monovalent and placebo recipients after each vaccination.
- American Indian or Alaska Native participants reported lower percentages of solicited systemic reactions among Original Monovalent recipients after each vaccination than in participants of other races.
- There were generally similar percentages and intensities of solicited systemic reactions after each vaccination among White, Asian, Black, or African American, Native Hawaiian/Other Pacific Islander, and multiple race participants in the Original Monovalent group.
- There were similar percentages and intensities of solicited systemic reactions after each vaccination among participants who are not Hispanic or Latino and participants who are Hispanic or Latino in the Original Monovalent group.

Table 77. Frequency and Percentage, by Subgroup, of Solicited Systemic Adverse Events within 7 Days After Dose 1 and Dose 2 by Demographic and Baseline Characteristics, Safety Analysis Set, Pediatric Expansion Study 301

Subgroup	Original Monovalent Any Grade n/N (%)	Original Monovalent ≥Grade 3 n/N (%)	Placebo Any Grade n/N (%)	Placebo ≥Grade 3 n/N (%)
All participants	--	--	--	--
Dose 1	948/1448 (65.5)	22/1448 (1.5)	207/726 (28.5)	4/726 (0.6)
Dose 2	1050/1394 (75.3)	118/1394 (8.5)	141/686 (20.6)	4/686 (0.6)
Age	--	--	--	--
Participants 12 to <15 years	--	--	--	--
Dose 1	638/970 (65.8)	16/970 (1.6)	152/487 (31.2)	2/487 (0.4)
Dose 2	708/935 (75.7)	79/935 (8.4)	108/461 (23.4)	3/461 (0.7)
Participants 15 to <18 years	--	--	--	--
Dose 1	310/478 (64.9)	6/478 (1.3)	55/239 (23.0)	2/239 (0.8)
Dose 2	342/459 (74.5)	39/459 (8.5)	33/225 (14.7)	1/225 (0.4)
Sex	--	--	--	--
Male	--	--	--	--
Dose 1[a]	427/744 (57.4)	5/744 (0.7)	102/405 (25.2)	1/405 (0.2)
Dose 2	484/702 (68.9)	51/702 (7.3)	58/386 (15.0)	2/386 (0.5)
Female	--	--	--	--
Dose 1[a]	521/704 (74.0)	17/ 704 (2.4)	105/321 (32.7)	3/321 (0.9)
Dose 2	566/692 (81.8)	67/692 (9.7)	83/300 (27.7)	2/300 (0.7)
Race	--	--	--	--
White	--	--	--	--
Dose 1	753/1093 (68.9)	15/1093 (1.4)	157/535 (29.3)	2/535 (0.4)
Dose 2	838/1057 (79.3)	96/1057 (9.1)	108/510 (21.2)	1/510 (0.2)
Black or African American	--	--	--	--
Dose 1	95/189 (50.3)	1/189 (0.5)	25/100 (25.0)	0/100 (0.0)
Dose 2	102/180 (56.7)	8/180 (4.4)	17/90 (18.9)	2/90 (2.2)
Asian	--	--	--	--
Dose 1	24/42 (57.1)	0/42 (0.0)	8/34 (23.5)	0/34 (0.0)
Dose 2	31/41 (75.6)	2/41 (4.9)	5/31 (16.1)	0/31 (0.0)
American Indian or Alaska Native	--	--	--	--
Dose 1	11/30 (36.7)	2/30 (6.7)	3/14 (21.4)	1/14 (7.1)
Dose 2	13/29 (44.8)	2/29 (6.9)	3/13 (23.1)	0/13 (0.0)
Native Hawaiian or other Pacific Islander	--	--	--	--
Dose 1	2/3 (66.7)	0/3 (0.0)	2/2 (100)	0/2 (0.0)
Dose 2	3/3 (100)	0/3 (0.0)	1/2 (50.0)	0/2 (0.0)
Mixed origin	--	--	--	--
Dose 1	55/81 (67.9)	1/81 (1.2)	11/36 (30.6)	1/36 (2.8)
Dose 2	56/76 (73.7)	7/76 (9.2)	6/35 (17.1)	1/35 (2.9)
Not reported	--	--	--	--
Dose 1	8/10 (80.0)	3/10 (30.0)	1/5 (20.0)	0/5 (0.0)
Dose 2	7/8 (87.5)	3/8 (37.5)	1/5 (20.0)	0/5 (20.0)

Subgroup	Original Monovalent Any Grade n/N (%)	Original Monovalent ≥Grade 3 n/N (%)	Placebo Any Grade n/N (%)	Placebo ≥Grade 3 n/N (%)
Ethnicity	--	--	--	--
Not Hispanic or Latino	--	--	--	--
Dose 1	785/1174 (66.9)	16/1174 (1.4)	174/591 (29.4)	2/591 (0.3)
Dose 2	875/1136 (77.0)	94/1136 (8.3)	118/558 (21.1)	4/558 (0.7)
Hispanic or Latino	--	--	--	--
Dose 1	159/269 (59.1)	6/269 (2.2)	33/135 (24.4)	2/135 (1.5)
Dose 2	171/253 (67.6)	24/253 (9.5)	23/128 (18.0)	0/128 (0.0)
Not reported	--	--	--	--
Dose 1	2/2 (100.0)	0/2 (0.0)	0/0 (0.0)	0/0 (0.0)
Dose 2	2/2 (100.0)	0/2 (0.0)	0/0 (0.0)	0/0 (0.0)

Source: 2019nCoV-301: Addendum 1.0 to 12-Month Adolescent CSR, Table 25, page 57-59
Abbreviations: COVID=coronavirus disease 2019; FDA=Food and Drug Administration; n=unique number of participants experiencing the adverse event; N=number of participants in the Safety Analysis Set within each treatment arm who received the dose and completed at least one day of the reactogenicity diary, reported an unsolicited adverse event that was mapped to a reactogenicity term within 7 days of the dose, reported a symptom in the paper memory aid of COVID symptoms that was mapped to a reactogenicity term within 7 days of the dose, or reported a temperature in the paper memory aid of COVID symptoms within 7 days of the dose
a. Original numbers for this category were incorrectly applied from the source table.
Note: Data were presented as number (%) of participants experiencing a solicited event. Percentages were based on n/N1 × 100 and n/N2 × 100. At each level of participant summarization, a participant was counted once if they indicated the event occurred and provided a severity during the reactogenicity period. The highest severity experienced during the reactogenicity period was summarized in this table.
Note: Grading of solicited adverse events was based on FDA Toxicity Grading Scale for Clinical Abnormalities

Clinical Reviewer Comment: In general, solicited systemic adverse events demonstrated similar trends when compared with local solicited adverse events (i.e. higher percentages of events in the vaccine groups verses placebo and higher percentages of events with subsequent doses). A key difference was the increase in percentages of Grade 4 events. Because this vaccine will be given as a single dose in both vaccinated and unvaccinated populations, it likely to improve the reactogenicity profile of the vaccine.

In general, the subgroups demonstrated similar trends compared with the overall safety population (i.e., higher percentages of events in the vaccinated group versus placebo and increasing percentages of events between Dose 1 and Dose 2).

Unsolicited Adverse Events

Pre-Crossover

During the pre-crossover vaccination period, there were similar percentages of participants in the Original Monovalent and placebo groups reporting unsolicited AEs across the Original Monovalent and placebo groups. Treatment-related unsolicited AEs were reported at a higher percentage in the Original Monovalent group than in the placebo group (3.0% vs 1.2%, respectively). No serious treatment-related unsolicited AEs were reported.

Most unsolicited AEs were mild or moderate in severity, with 0.5% of Original Monovalent recipients and 0.8% of placebo recipients experiencing severe AEs (see table below).

Table 78. Frequency and Percentage of Unsolicited Adverse Events During the Pre-Crossover Vaccination Period, Safety Analysis Set, Pediatric Expansion Study 301

Adverse Event Category	Original Monovalent N=1487 n (%)	Placebo N=745 n (%)
Any TEAEs	239 (16.1)	124 (16.6)
Any severe TEAE[a]	8 (0.5)	6 (0.8)
Any treatment-related TEAE[a]	44 (3.0)	9 (1.2)
Any severe treatment-related TEAE[a]	0	0
Any MAAE	95 (6.4)	50 (6.7)
Any treatment-related MAAE[a]	5 (0.3)	3 (0.4)
Any serious treatment-related MAAE[a]	0	0
Any serious TEAE	7 (0.5)	2 (0.3)
Any serious treatment-related TEAE[a]	0	0
Any TEAE leading to vaccination discontinuation	2 (0.1)	1 (0.1)
Any treatment-related TEAE leading to vaccination discontinuation[a]	1 (<0.1)	0
Any TEAE leading to study discontinuation	0	0
Any treatment-related TEAE leading to study discontinuation[a]	0	0
Any AESI: PIMMC (Site Reported)	0	0
Any AESI: PIMMC (Protocol Defined)	1 (<0.1)	0
Any AESI: PIMMC (Site Reported or Protocol Defined)	1 (<0.1)	0
Any treatment-related AESI: PIMMC (Protocol Defined)[a]	0	0
Any treatment-related AESI: PIMMC (Site Reported)[a]	0	0
Any treatment-related AESI: PIMMC (Site Reported or Protocol Defined)[a]	0	0
Any AESI: relevant to COVID-19	0	0
Any treatment-related AESI: relevant to COVID-19[a]	0	0
Death	0	0

Source: eSub3 CSR Addendum to 12-Month Adolescent CSR, Table 80, Pg. 10-11
Abbreviations: AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; PIMMC=potential immune- mediated medical conditions; TEAE=treatment- emergent adverse event; N=The Safety Analysis Set, included all participants who received at least 1 dose of trial vaccine. Participants in the Safety Analysis Set were analyzed according to the treatment actually received; n=number of unique participants in each category.
a. Relationship and severity were based on the data reported by site, i.e., missing information was not imputed.

During the pre-crossover vaccination period, the percentage of participants reporting unsolicited AEs within 49 days of the first vaccination was similar between Original Monovalent recipients (15.9%) and placebo (16.5%), see table below.

The percentages of participants with unsolicited AEs by SOC and PT were generally similar between the Original Monovalent and placebo groups, with the exception of events of the SOC Gastrointestinal Disorders, which were reported more frequently for placebo recipients (2.7%) than Original Monovalent recipients (1.7%), events of SOC Infections and infestations, which were reported more frequently for placebo recipients (5.4%) than Original Monovalent recipients (4.2%) and events of SOC General disorders and administration site conditions which were reported more frequently for Original Monovalent recipients (2.8%) than placebo recipients (1.9%).

Table 79. Frequency and Percentage of Unsolicited Adverse Events Occurring in ≥0.5% of Participants Within 49 Days of First Vaccination in Pre-Crossover Vaccination Period, Safety Analysis Set, Pediatric Expansion Study 301

System Organ Class/ Preferred Term	Original Monovalent N=1487 n (%)	Placebo N=745 n (%)
Any TEAE within 49 days of vaccination	237 (15.9)	123 (16.5)
Blood and lymphatic system disorders	11 (0.7)	0
Lymphadenopathy	11 (0.7)	0
Eye disorders	7 (0.5)	1 (0.1)
Gastrointestinal Disorders	25 (1.7)	20 (2.7)
Diarrhea	8 (0.5)	7 (0.9)
Nausea	8 (0.5)	6 (0.8)
Vomiting	5 (0.3)	6 (0.8)
Infections and Infestations	63 (4.2)	40 (5.4)
Nasopharyngitis	6 (0.4)	6 (0.8)
Upper respiratory tract infection	10 (0.7)	13 (1.7)
Viral infection	11 (0.7)	6 (0.8)
Respiratory, thoracic, and mediastinal disorders	52 (3.5)	32 (4.3)
Nasal congestion	32 (2.2)	17 (2.3)
Cough	23 (1.5)	10 (1.3)
Dyspnea	3 (0.2)	4 (0.5)
Oropharyngeal pain	25 (1.7)	17 (2.3)
Rhinorrhea	21 (1.4)	14 (1.9)
General disorders and administration site conditions	42 (2.8)	14 (1.9)
Chills	7 (0.5)	4 (0.5)
Fatigue	12 (0.8)	6 (0.8)
Pain	3 (0.2)	2 (0.3)
Pyrexia	10 (0.7)	5 (0.7)
Nervous system disorders	34 (2.3)	20 (2.7)
Headache	25 (1.7)	14 (1.9)
Musculoskeletal and connective tissue disorders	24 (1.6)	3 (0.4)
Skin and subcutaneous tissue disorders	22 (1.5)	7 (0.9)
Rash	7 (0.5)	2 (0.3)
Injury, poisoning and procedural complications	40 (2.7)	15 (2.0)
Skin laceration	1 (<0.1)	5 (0.7)
Psychiatric disorders	21 (1.4)	9 (1.2)
Attention deficit hyperactivity disorder	8 (0.5)	2 (0.3)

Source: eSub3 CSR Addendum to 12-Month Adolescent CSR, Table 80, Pg. 18
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants in the Safety Analysis Set within each treatment; TEAE=treatment- emergent adverse event; n=number of unique participants in each category.
Percentages or incidence proportion was based on n/N*100. Adverse Events coded using MedDRA version 25.0.

Clinical Reviewer Comment: In general, the percentages of participants who reported unsolicited adverse events within 49 days of the first vaccination (i.e., 28 days after Dose 2 of the 2-dose series) were balanced between the vaccine and placebo groups in the pre-crossover period. These data do not raise any safety concerns.

In the subgroup analyses for the Pre-Crossover Vaccination Period, the percentages of participants with unsolicited adverse events were similar between males (15.3%) and females (16.6%) and between individual 12 to <15 years of age (17.8%) and individuals 15 to <18 years of age (12.2%). For subgroup analysis by race, the percentages of participants with unsolicited adverse events were highest for White (17.0%) and Native Hawaiian or Other Pacific Islander (33.3%) participants. For ethnicity, the percentages of individuals with unsolicited adverse

events were highest in Not Hispanic or Latino (17.1%) participants. In general, no safety concerns were identified in the subgroup analysis that were not seen in the overall safety population.

Post-Crossover

During the post-crossover vaccination period, a higher percentage of Placebo to Original Monovalent participants (24.5%) reported unsolicited AEs than Original Monovalent to Placebo recipients (17.9%). Treatment-related unsolicited AEs were also reported by a higher percentage of participants in the Placebo to Original Monovalent group than in the Original Monovalent to placebo group (7.2% vs 1.3%, respectively). One participant experienced a serious treatment-related unsolicited AE (myocarditis, discussed in Section 6.2.12.5).

Most unsolicited AEs were mild or moderate in severity, with 3.6% of Placebo to Original Monovalent recipients and 2.3% of Original Monovalent to Placebo recipients experiencing severe AEs (see table below).

Table 80. Frequency and Percentage of Unsolicited Adverse Events During the Post-Crossover Vaccination Period, Safety Analysis Set, Pediatric Expansion Study 301

Adverse Event Category	Placebo to Original Monovalent N=666 n (%)	Original Monovalent to Placebo N=1354 n (%)
Any TEAEs	163 (24.5)	242 (17.9)
Any severe TEAE[a]	24 (3.6)	31 (2.3)
Any treatment-related TEAE[a]	48 (7.2)	17 (1.3)
Any severe treatment-related TEAE[a]	1 (0.2)	0
Any MAAE	49 (7.4)	112 (8.3)
Any treatment-related MAAE[a]	3 (0.5)	2 (0.1)
Any serious treatment-related MAAE[a]	1 (0.2)	0
Any serious TEAE	8 (1.2)	11 (0.8)
Any serious treatment-related TEAE[a]	1 (0.2)	0
Any TEAE leading to vaccination discontinuation	1 (0.2)	0
Any treatment-related TEAE leading to vaccination discontinuation[a]	0	0
Any TEAE leading to study discontinuation	0	0
Any treatment-related TEAE leading to study discontinuation[a]	0	0
Any AESI: PIMMC (Site Reported)	0	1 (<0.1)
Any AESI: PIMMC (Protocol Defined)	1 (0.2)	2 (0.1)
Any AESI: PIMMC (Site Reported or Protocol Defined)	1 (0.2)	2 (0.1)
Any treatment-related AESI: PIMMC (Site Reported)[a]	0	0
Any treatment-related AESI: PIMMC (Protocol Defined)[a]	1 (0.2)	0
Any treatment-related AESI: PIMMC (Site Reported or Protocol Defined)[a]	1 (0.2)	0
Any AESI: relevant to COVID-19	0	0
Any treatment-related AESI: relevant to COVID-19[a]	0	0
Death	0	0

Source: eSub3 CSR Addendum to 12-Month Adolescent CSR, Table 4, Page 13
Abbreviations: AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; PIMMC=potential immune- mediated medical conditions; TEAE=treatment-emergent adverse event; N=Number of participants in the Safety Analysis Set within each treatment; n=number of unique participants in each category.
a. Relationship and severity were based on the data reported by site, i.e., missing information was not imputed.

During the post-crossover vaccination period, the percentage of participants reporting unsolicited AEs reported within 49 days of the first vaccination occurred at a higher percentage

among Placebo to Original Monovalent recipients (23.9%) than Original Monovalent to Placebo recipients (17.4%) (see table below).

The percentages of participants with unsolicited AEs by SOC were generally higher among the Placebo to Original Monovalent recipients than Original Monovalent to Placebo recipients for SOCs comprising PTs consistent with reactogenicity TEAEs (including events of pain, injection site pain, pyrexia, and fatigue).

Table 81. Frequency and Percentage of Unsolicited Adverse Events Occurring in ≥0.5% of Participants Within 49 Days of First Vaccination in Post-Crossover Vaccination Period, Safety Analysis Set, Pediatric Expansion Study 301

System Organ Class/ Preferred Term	Post-Crossover Placebo to Original Monovalent N=666 n (%)	Post-Crossover Original Monovalent to Placebo N=1354 n (%)
Any AE within 49 days of vaccination	159 (23.9)	235 (17.4)
Gastrointestinal Disorders	28 (4.2)	33 (2.4)
Diarrhea	8 (1.2)	10 (0.7)
Nausea	23 (3.5)	20 (1.5)
Vomiting	19 (2.9)	18 (1.3)
Infections and Infestations	29 (4.4)	93 (6.9)
Upper respiratory tract infection	10 (1.5)	28 (2.1)
Viral infection	8 (1.2)	19 (1.4)
Respiratory, thoracic, and mediastinal disorders	59 (8.9)	106 (7.8)
Nasal congestion	38 (5.7)	73 (5.4)
Cough	29 (4.4)	50 (3.7)
Dyspnea	2 (0.3)	10 (0.7)
Oropharyngeal pain	27 (4.1)	63 (4.7)
Rhinorrhea	36 (5.4)	69 (5.1)
Chills	28 (4.2)	15 (1.1)
Fatigue	20 (3.0)	27 (2.0)
Injection site erythema	3 (0.5)	0
Injection site swelling	6 (0.9)	0
Malaise	6 (0.9)	0
Injection site pain	11 (1.7)	7 (0.5)
Pain	24 (3.6)	13 (1.0)
Pyrexia	35 (5.3)	15 (1.1)
Nervous system disorders	51 (7.7)	53 (3.9)
Ageusia	3 (0.5)	5 (0.4)
Anosmia	3 (0.5)	6 (0.4)
Headache	44 (6.6)	45 (3.3)
Musculoskeletal and connective tissue disorders	25 (3.8)	19 (1.4)
Myalgia	20 (3.0)	14 (1.0)
Skin and subcutaneous tissue disorders	7 (1.1)	11 (0.8)
Urticaria	3 (0.5)	1 (<0.1)

System Organ Class/ Preferred Term	Post-Crossover Placebo to Original Monovalent N=666 n (%)	Post-Crossover Original Monovalent to Placebo N=1354 n (%)
Injury, poisoning, and procedural complications	8 (1.2)	26 (1.9)
Investigations	3 (0.5)	1 (<0.1)
Psychiatric disorders	5 (0.8)	15 (1.1)
Vascular disorders	3 (0.5)	1 (<0.1)
Hot flush	3 (0.5)	1 (<0.1)

Source: eSub3 CSR Addendum to 12-Month Adolescent CSR, Table 13, 26-27
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N=Number of participants in the Safety Analysis Set within each treatment; n=number of unique participants in each category.
Percentages or incidence proportion was based on n/N*100. Adverse Events coded using MedDRA version 25.0.

Reviewer Comment: While the overall percentages of participants who experienced any unsolicited adverse events within 49 days of first vaccination were slightly higher in the Placebo to Original Monovalent group compared with the Original Monovalent to Placebo group, the individual Preferred Terms were reasonably balanced. These data are reassuring.

In the subgroup analyses for the Post-Crossover Vaccination Period, no safety concerns were identified that were not seen in the overall safety population.

Booster (Original Monovalent)

Unsolicited AEs through 28 days after the booster vaccination and through the data cutoff date were reported in 6.4% and 7.5% of adolescent participants, respectively. Most unsolicited AEs were mild or moderate in severity, with severe AEs in <2.0% of participants. Most severe AEs were reported >28 days after booster vaccination. Most unsolicited AEs were assessed by the investigator as not related to study vaccine, with 1 (<0.1%) participant who experienced a severe treatment-related AE within 28 days after booster vaccination. Few participants reported SAEs, most were reported >28 days after booster vaccination, and none were considered treatment-related. There were no deaths. One participant reported an AE leading to study discontinuation. No participant reported a PIMMC or AESIs relevant to COVID-19. MAAEs through 28 days after the booster dose and through the data cutoff date were reported in 2.5% and 3.5% of participants, respectively, with treatment-related MAAEs reported in few (0.2%) participants.

Table 82. Frequency and Percentage of Unsolicited Adverse Events From Start of Booster Vaccination With Original Monovalent Through 28 Days After Booster Vaccination and From Start of Booster Vaccination Through the Data Cutoff Date, Booster Safety Analysis Set and Safety Analysis Set, Pediatric Expansion Study 301

Adverse Event Category	Original Monovalent Booster Through 28 Days Post Booster N=1499 n (%)	Original Monovalent Booster Through Data Cutoff Date[a] N=1499 n (%)
Any AE	96 (6.4)	113 (7.5)
Any severe AE[b]	15 (1.0)	25 (1.7)
Any treatment-related AEb[2]	17 (1.1)	17 (1.1)
Any severe treatment-related AE[b]	1 (<0.1)	1 (<0.1)
Any MAAE	38 (2.5)	52 (3.5)
Any treatment-related MAAE[b]	3 (0.2)	3 (0.2)
Any serious treatment-related MAAE[b]	0	0

Adverse Event Category	Original Monovalent Booster Through 28 Days Post Booster N=1499 n (%)	Original Monovalent Booster Through Data Cutoff Date[a] N=1499 n (%)
Any SAE	2 (0.1)	19 (1.3)
Any treatment-related SAE[b]	0	0
Death	0	0
Any AE leading to study discontinuation	0	1 (<0.1)
Any treatment-related AE leading to study discontinuation[b]	0	0
Any AESI: PIMMC (site reported)	0	0
Any AESI: PIMMC (protocol defined)	0	0
Any AESI: PIMMC (Site reported or protocol defined)	0	0
Any AESI: relevant to COVID-19	0	0

Source: eSub3 CSR Addendum to 6-Month Booster Safety Addendum to 2019nCoV-301 12-Month Adolescent Clinical Study Report, Table 1, Page 7-8

Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; MAAE=medically attended adverse event; n=number of participants at each level of summarization; PIMMC=potential immune-mediated medical conditions;

The Booster Safety Analysis Set includes all participants in the safety analysis set who received a dose during the booster portion of the study.

a. Note: The data cutoff date for the 6-month booster safety analysis was 12 November 2022.

b. Relationship and severity were based on the data reported by site, i.e., missing information was not imputed.

Note: If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), then it was recorded as an AE with the start date the 7th day following the relevant study vaccination and followed to resolution. These Solicited AEs that continued past Day 6 were not included in this summary. At each level of participant summarization, a participant was counted once if the participant reported one or more events.

Unsolicited TEAEs through 28 days following the booster dose were reported for 96 (6.4%) participants, which was less than for the Original Monovalent recipients during either the pre-crossover (15.9%) or the Placebo to Original Monovalent group during the post-crossover (24.5%) vaccination periods through 28 days following the 2-dose series (i.e., within 49 days of the first vaccination). Unsolicited TEAEs through the data cutoff date (12 November 2022) were reported for 113 (7.5%) participants. Unsolicited TEAEs of the SOC Infections and Infestations (2.0%) were the most frequently reported through 28 days following the booster dose. PT, the most frequent TEAEs (incidence ≥0.5%) through 28 days and through data cutoff following the booster dose were rhinorrhea (1.3%), oropharyngeal pain (1.3%), and nasal congestion (1.3%).

In the subgroup analyses for the Booster Vaccination Period, the percentages of participants with unsolicited adverse events were similar between males (6.7%) and females (6.1%) and between individual 12 to <15 years of age (6.7%) and individuals 15 to <18 years of age (5.8%). Subgroup analysis by race was difficult to interpret due to low numbers of participants in several racial groups. The percentages of individuals with unsolicited adverse events were balanced between ethnic groups.

6.2.12.3 Deaths

No deaths were reported in either the initial or blinded crossover vaccination periods through 12 months of safety follow-up. No deaths were reported through 28 days following the booster vaccination.

6.2.12.4 Nonfatal Serious Adverse Events

Pre-Crossover

SAEs that adolescent participants reported in the Original Monovalent group were analyzed by SOC and PT compared with the placebo group. During the pre-crossover vaccination period,

frequencies of SAEs reported were reported in 7 (0.5%) participants in the Original Monovalent (0.5%) compared with 2 (0.3%) participants in the placebo group. SAEs of the SOC Injury, poisoning and procedural complications (0.2%) were most frequently reported in the Original Monovalent group. Within this SOC, PTs included 2 (0.1%) participants with intentional overdose and 1 participant (<0.1%) with splenic rupture. There were no medically-attended SAEs assessed as related to a study vaccine.

Clinical Reviewer Comment: Although SAEs occurred at a slightly higher percentage in participants who received the 2-dose study vaccine compared with placebo, few adolescent participants experienced SAEs overall, and the safety profile is reassuring.

Post-Crossover

During the post-crossover vaccination period, percentages of SAEs reported were higher in the crossover group that received the Original Monovalent vaccine (1.4%) compared with the group that crossed from Original monovalent to placebo (0.9%). SAEs of the SOC Psychiatric disorders (0.6%) were most frequently reported in both the Placebo to Original Monovalent and Original Monovalent to Placebo groups during the crossover vaccination period.

Clinical Reviewer Comment: There were 12 participants who experienced psychiatric disorders, and 7 of these had either suicidal ideation (5 participants) or made a suicide attempt (2 participants). The overall percentage of these participants is low and unlikely to be above the background rate for adolescent psychiatric disorders, particularly suicidal ideation with or without an attempt. The narrative information for these 12 cases was reviewed, and these events either lacked a temporal relationship to vaccine administration or the participant had a history of psychiatric condition(s) which provided plausible alternative explanations for these conditions and/ or events. It is the assessment of this reviewer that these SAEs involving psychiatric disease and/ or suicidal ideation in adolescents are not related to the study vaccine.

Booster

A total of 19 (1.3%) out of 1,499 adolescent participants reported SAEs from the time of booster vaccination through the data cutoff date of November 12, 2022 (6 months of safety follow-up) with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). SAEs under the SOC Psychiatric Disorders were the most frequent (incidence 0.6%) among adolescent participants through the data cutoff date, and within this SOC, each PT was reported in 1 (<0.1%) participant. There were no SAEs considered related to the study vaccine through the data cutoff date. There were no reports of SAEs of interest (i.e., myocarditis/pericarditis and anaphylaxis) during the booster vaccination period.

Clinical Reviewer Comment: During the booster vaccination period, the percentage of participants reporting SAEs was similar or lower compared with the percentages of participants who reported SAEs during the pre- and post-crossover vaccination periods (0.5% vs 1.4% vs. 0.6% in the pre-crossover vs. post-crossover placebo to Original Monovalent vs. booster vaccination periods, respectively). SAEs of the SOC Psychiatric disorders (0.6%) were most frequently reported during the booster vaccination period. While there were no trends toward specific psychiatric events being reported as SAEs through the data cutoff date that were considered related to the study vaccine, there was a predominance of neuropsychiatric events that may reflect the increasing incidence of mental health issues in the U.S. among adolescents. All available narrative information that the Applicant provided for the psychiatric conditions that occurred during the Booster Vaccination period was reviewed. In general, the psychiatric SAEs were more temporally

associated to vaccination during the Booster Vaccination Period than the preceding vaccination periods; however, most participants, including the ones with suicidal ideation or attempt, had a history of psychiatric conditions that confounded the relationship of these conditions or events to vaccine administration. It is also unlikely that the percentages of participants with psychiatric conditions exceed the respective background rates, particularly for suicidal ideation and suicide attempt. It is the assessment of this reviewer that these SAEs involving psychiatric disease and/or suicidal ideation in adolescents during the booster vaccination period are not related to the study vaccine. Therefore, psychiatric conditions do not appear to be a safety signal following administration of this vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

Myocarditis/Pericarditis

During the initial vaccination period, no participants in the Original Monovalent group or the placebo group reported an adverse event of myopericarditis.

During the blinded crossover vaccination period, 1 participant in the Original Monovalent group reported a serious adverse event of myocarditis, and there were no reports of myocarditis in the placebo group. A summary of the narrative is as follows:

> *A 16-year-old White male from the U.S. who received 2 doses of the Original monovalent vaccine during the post-crossover period experienced a treatment-related SAE of myocarditis. Approximately 2 days after Dose 2 (and 42 days after Dose 1), he reported fever (101°F), malaise/weakness/lethargy, nausea/vomiting, constant moderate anterior chest pain, and the sensation that his heart was racing. He presented to the emergency department; SARS-CoV-2 PCR test was negative, serum troponin was elevated at 21,396.5 ng/L, an EKG showed evidence of acute pericarditis, and echocardiogram showed left ventricular ejection fraction of 50%. Per cardiology, he was discharged home on hospital Day 4 after troponin levels had declined, echocardiogram showed a normal left ventricular ejection fraction of 60.7%, and he had no chest pain at rest or with ambulation. The event was considered resolved after a follow-up visit with cardiology approximately 4 months after the onset of symptoms.*

There were no cases of myocarditis or pericarditis identified during the booster vaccination period.

Anaphylaxis

There were no cases reported during the initial or blinded crossover vaccination periods through 12 months of safety follow-up and through 28 days following the booster vaccination.

6.2.12.7 Dropouts and/or Discontinuations

AEs Leading to Discontinuation

During the pre-crossover vaccination period, there were 3 cases of unsolicited AEs leading to discontinuation of study vaccination (i.e., within 7 or 28 days of any dose or through the data cut-off date): 2 participants in the Original Monovalent group (1 due to moderate headache assessed as related to the vaccine and 1 due to moderate juvenile myoclonic epilepsy considered unrelated to study vaccine) and 1 participant in the placebo group who discontinued study vaccination due to mild rhinorrhea assessed as unrelated to study vaccine.

During the post-crossover vaccination period, there was 1 participant from the placebo group who had severe malnutrition (assessed as unrelated to study vaccine) leading to discontinuation of study vaccination.

During the booster vaccination period, there were no cases of AEs leading to discontinuation of study vaccination.

AEs Leading to Study Withdrawal

During the pre-crossover vaccination period, there were no cases of AEs leading to study withdrawal across the Original Monovalent and placebo groups.

During the post-crossover vaccination period, there were 2 cases of AEs leading to study withdrawal in the booster period (1 case of acute anxiety and 1 case of lipoma). None of these cases were considered related to study intervention.

6.2.13 Study Summary and Conclusions

Effectiveness

Pediatric Expansion Study 301 provides both immunogenicity data and descriptive efficacy data that support the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) as a 2-dose series administered 21 days apart in seronegative individuals 12 through 17 years of age. First, immunogenicity data from this study met all pre-specified noninferiority success criteria (in terms of GMTR and difference in SCR) to demonstrate noninferiority of neutralizing antibody immune responses to the 2-dose series in 12 through 17-year-old participants compared with those in adult participants 18 through 25 years of age in whom clinical efficacy had been demonstrated (see Section 6.1 Adult Main Study 301). Vaccine effectiveness can be inferred from these noninferiority immunobridging analyses. Second, although this adolescent study was not sufficiently powered to establish vaccine efficacy of the Original monovalent vaccine in this population, descriptive efficacy analysis yielded a VE of 79.8% (95% CI: 47.6, 92.2) for preventing symptomatic mild, moderate, or severe COVID-19 in baseline seronegative adolescent participants (see Table 70 in Section 6.2.11.3).

Effectiveness of a homologous “booster” with Novavax COVID-19 Vaccine (Original monovalent) in adolescents 12 through 17 years of age who had already received the 2-dose series was then inferred based on immunobridging analyses demonstrating noninferiority between immune responses to the 2-dose series and immune responses to the 3rd dose.

Safety

Data from Pediatric Expansion Study 301 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) when administered as a 2-dose series and as a single-dose homologous “booster” (3rd dose) in individuals 12 years through 17 years of age. In this study of 2,153 participants 12 through 17 years1 of age who received at least one dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), no vaccine-related SAEs or new safety signals were identified.

In the pre-crossover period, local and systemic adverse reactions solicited in the 7 days following each dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had increasing rates with each dose, from 65.3% of participants reporting injection site pain/tenderness after Dose 1 to 75.0% of participants reporting injection site pain/ tenderness after Dose 2. Grade 3 events were most frequently reported for solicited ARs of fatigue/malaise, myalgia, and headache.

The percentage of Grade 3 ARs increased after the 3rd dose of Novavax COVID-19 Vaccine for each solicited adverse reaction (except fever) when compared with both the first and second doses. A total of 40.5% of participants reported any Grade 3 solicited AR following the 3rd dose. In contrast, approximately 0.4% of participants had Grade 4 systemic solicited AR after the third vaccine dose (0.4% overall). While contemporaneous comparisons of solicited ARs between individuals 18 years of age and older and individuals 12 through 17 years of age are not available, the percentage of participants 12 through 17 years of age reporting solicited severe ARs after 3 doses is generally higher than for participants 18 years of age and older.

In this study, there were no deaths, and no safety signals were identified in unsolicited AEs or SAEs. The numbers of AEs leading to discontinuation (4 participants) or study withdrawal (1 participant) were low. One case of myocarditis/ pericarditis was reported, and this case is included in the USPI. Postmarketing safety studies evaluating myocarditis/pericarditis are ongoing. In summary, solicited ARs were commonly reported in participants 12 through 17 years of age, with a high percentage of participants 12 through 17 years of age reporting local and systemic solicited adverse reactions after three doses (77% and 80%, respectively). Information on the number and percentage of participants 12 through 17 years of age with solicited local and systemic ARs by severity will be communicated in the USPI.

Overall, the updated safety information for Pediatric Expansion Study 301 supports approval of the vaccine, and the risk-benefit assessment for this vaccine technology is still favorable.

6.3 Study 311, Part 1

NCT05372588

Title: 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

The sections below summarize immunogenicity and safety data from Study 311 Part 1, in which participants previously vaccinated with 2 or 3 doses of an mRNA COVID-19 vaccine (any combination of the Moderna and/ or Pfizer-BioNTech COVID-19 vaccines Original monovalent) were randomized to receive Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.1), or bivalent vaccine (Original and Omicron BA.1). Each vaccine contained a total of 5 µg of antigen and 50 µg of Matrix-M adjuvant. The analysis includes data collected from the study enrollment start date of May 31, 2022, through the study stop date of June 28, 2023, with a data extraction date of October 18, 2023, in 951 participants 18 through 64 years of age (8 months of follow-up).

6.3.1 Objectives

The primary objective of Study 311 Part 1 was to determine if the monovalent vaccine (Omicron BA.1) induced superior neutralizing antibody responses to the Omicron BA.1 sublineage compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in participants previously vaccinated with 3 doses of the Moderna and/ or Pfizer-BioNTech original monovalent mRNA COVID-19 vaccines.

Secondary objectives were as follows:

- To determine if the bivalent vaccine (Original and Omicron BA.1) induced noninferior neutralizing antibody responses to the Omicron BA.1 sublineage compared with the

neutralizing antibody responses induced by the monovalent vaccine (Omicron BA.1)

- To determine if the bivalent vaccine (Original and Omicron BA.1) induced noninferior neutralizing antibody responses to the ancestral (Wuhan) strain compared with the neutralizing antibody responses induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
- To assess the overall safety of 1-dose regimens of monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), or bivalent vaccine (Original and Omicron BA.1)

6.3.2 Design Overview

Study 311 Part 1 was a Phase 3, randomized, observer-blinded study conducted in adults 18 to 64 years of age.

A total of 122 participants who had received 2 previous doses of an mRNA COVID-19 vaccine, with the last dose administered ≥180 days prior to study vaccination, were randomized 1:1 to one of 2 groups in which they received a single dose of study vaccine:

- Group A: Single dose of monovalent vaccine (Omicron BA.1) (n=61)
- Group B: Single dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (n=61).

Data from individuals randomized to Groups A and B were not included in the analysis of the study's primary objective and endpoints. Per the study protocol, primary analyses were based solely on data from individuals randomized to Groups C, D, and E, all of whom had received 3 previous doses of an mRNA COVID-19 vaccine, with the last dose administered ≥90 days prior to randomization. A total of 831 medically stable adult participants were randomized 1:1:1 to one of 3 groups in which they received a single dose of study vaccine:

- Group C: Single dose monovalent vaccine (Omicron BA.1) (n=279)
- Group D: Single dose Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (n=274)
- Group E: Single dose bivalent vaccine (Original and Omicron BA.1) (n=278)

6.3.3 Population

The study enrolled nonpregnant, non-lactating individuals between 18 and 64 years of age at screening who were willing and able to give informed consent prior to study enrollment and to comply with study procedures, were medically stable, who agreed not to participate in any other SARS-CoV-2 prevention or treatment trials for the duration of the study, and who had previously received 2 or 3 doses of the Moderna and/or Pfizer-BioNTech COVID-19 prototype vaccines.

Pertinent Exclusion Criteria

- Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy.
- Chronic administration (defined as >14 continuous days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days prior to study vaccination.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The 3 study treatments were Matrix-M-adjuvanted, SARS-Co-V-2 recombinant spike (rS) protein-based COVID-19 vaccines, each containing 5 µg of SARS-CoV-2 rS antigen with 50 µg Matrix-M adjuvant, administered as an intramuscular injection:

- NVX-CoV2515 monovalent vaccine (Omicron BA.1): coformulated Omicron BA.1 SARS-CoV-2 rS vaccine with Matrix-M adjuvant
    - Dose 0.5mL (5 µg/ 50 µg), lot # 5162Z001
- Original Monovalent Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent): coformulated prototype SARS-CoV-2 rS vaccine with Matrix-M adjuvant
    - Dose 0.5mL (5 µg/ 50 µg), lot # 4302MF003
- Original Monovalent + NVX-CoV2515 bivalent vaccine (Original and Omicron BA.1): Site-mixed NVXCoV2373 + NVXCoV2515, each coformulated with Matrix-M adjuvant
    - Dose 0.5mL (5 µg/ 50 µg [total]), lot # 5162Z001 and 4302MF003

6.3.5 Directions for Use

One intramuscular injection of monovalent vaccine (Omicron BA.1) or Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or bivalent vaccine (Original and Omicron BA.1) was administered on Day 0 by qualified study site personnel according to standard practice as directed in the Pharmacy Manual.

6.3.6 Sites and Centers

Participants were enrolled at 18 clinical sites in Australia.

6.3.7 Surveillance/Monitoring

Immunogenicity (Laboratory Assays)

Blood samples for immunogenicity assessments were collected and analyzed before vaccination on Day 0 and on Days 7, 14, and 28. Blood samples were analyzed for Omicron BA.1 sublineage and ancestral (Wuhan) strain neutralizing antibody geometric mean titers (GMTs) and seroresponse rates (SRRs [percentage of participants who achieve ≥4-fold increase in neutralizing antibody titers from baseline on Day 0]). Samples were analyzed using validated microneutralization assays with an inhibitory dilution of 50% (ID_{50}) to determine Omicron BA.1 sublineage-specific and ancestral (Wuhan) strain-specific neutralizing antibody titers.

Safety Monitoring

Participants remained under observation for at least 30 minutes postvaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants used an eDiary to record reactogenicity (solicited AEs) for 7 days starting on the day of vaccination.

Unsolicited AEs were collected through Day 28 postvaccination. Collection of treatment-related medically attended adverse events (MAAEs), adverse event of special interest (AESIs), and serious adverse events (SAEs) were collected through Day 240 days postvaccination. AESIs included myocarditis/pericarditis, potential immune-mediated medical condition (PIMMCs), and complications of COVID-19.

6.3.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints:

Immunogenicity of a single dose of the monovalent vaccine (Omicron BA.1) and a single dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was assessed using the following prespecified co-primary endpoints:

- Neutralizing antibody GMTs against the BA.1 sublineage at Day 14
- SRRs against the BA.1 sublineage at Day 14
- Two secondary immunogenicity endpoints (neutralizing antibody GMTs and SRRs against the ancestral (Wuhan) strain were used to make comparisons between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to conduct superiority and noninferiority analyses between the monovalent vaccine (Omicron BA.1) and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).
- Using neutralizing antibody GMTs against the Omicron BA.1 sublineage, superiority was defined by a lower bound of 2-sided 95% confidence interval (CI) for the geometric mean titer ratio (GMTR) of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is greater than 1.0.
- Noninferiority of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was assessed based on the percentage difference of SRRs against the Omicron BA.1 sublineage. The criterion for noninferiority was a lower bound of the two-sided 95% CI of the estimated percentage difference in SRRs (Omicron BA.1 minus [Original monovalent]) greater than -5%.
- Noninferiority of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for neutralizing antibody GMTs against the ancestral (Wuhan) strain. Criterion for noninferiority is met if the GMTR is greater than 0.67 (i.e., lower bound of 2-sided 95% confidence interval (CI) for GMTR is >0.67, representing a 1.5-fold difference).
- Noninferiority of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) by percentage difference of SRRs against the ancestral (Wuhan) strain. Criterion for noninferiority by the percentage difference in SRRs is met if the percentage difference in SRRs is greater than -10% (i.e., lower bound of the two-sided 95% CI >-10%).

Similar immunogenicity endpoints and criteria for superiority and noninferiority as those described above were used to descriptively analyze the monovalent vaccine (Omicron BA.1) on Day 28 and the bivalent vaccine (Original and Omicron BA.1) on Day 14 and 28 compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

Additional secondary endpoints were descriptively analyzed to assess neutralizing antibody responses generated by the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.1) against the Omicron BA.1 sublineage over time over time from Day 0 to Day 240 after vaccination.

Exploratory endpoints were descriptively analyzed to assess neutralizing antibody responses to other SARS-CoV-2 variants.

Safety Endpoints:

- 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 following vaccination
- Incidence and relationship of MAAEs, AESIs (predefined list including PIMMCs, myocarditis and/or pericarditis, and complications specific to COVID-19), and SAEs through 240 days following vaccination

6.3.9 Statistical Considerations & Statistical Analysis Plan

Please see Section 6.3.8 for the immunogenicity statistical analysis plan.

AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using System Organ Class (SOC) and Preferred Term (PT) according to MedDRA.

6.3.10 Study Population and Disposition

Available data were from participants enrolled in the study from the start date of May 31, 2022, through the stop date of June 28, 2023.

6.3.10.1 Populations Enrolled/Analyzed

- Randomized Population: All participants who were enrolled and randomized, regardless of whether they received any study vaccine (a total of 953 participants randomized to groups A, B, C, D, and E).
- Immunogenicity population: all randomized participants who received the study vaccine according to protocol, had no major protocol deviations or events (e.g., COVID-19 infection) considered clinically relevant to impact immunogenicity responses, and who completed the study blood tests. Only the immunogenicity population from groups C, D, and E are included in the per-protocol analyses of the study's primary immunogenicity endpoints.
- The Per-Protocol (PP) Analysis Set included the subset of participants who tested negative for prior SARS-CoV-2 infection [tested via both anti-N (nucleocapsid) serology and PCR at the beginning of the study prior to vaccination, a total of 356 participants on Day 14 and 335 participants on Day 28 in groups C, D, and E)]. While the study protocol specified that analysis of the primary immunogenicity endpoints would be performed using the PP Analysis Set, the protocol also planned additional analyses using a Per-Protocol Analysis Set 2 (PP2) to examine the effect of including participants with serologic evidence of prior SARS-CoV-2 infection based on a positive baseline anti-N result (n=766 on Day 14; n=698 on Day 28).
- Safety population: all randomized participants who received 1 dose of study vaccine, regardless of protocol violations or missing data (a total of 951 participants in groups A, B, C, D, and E). All 122 randomized participants in Groups A and B received a study vaccine and were included in the Safety Analysis Set. Of the 831 randomized participants in Groups C, D, and E, 829 received a study vaccine and were included in the Safety Analysis Set.

6.3.10.1.1 Demographics

The table below presents the participant demographics and baseline disease characteristics in the Safety Analysis Set.

Table 83. Participant Demographics and Baseline Disease Characteristics, Safety Analysis Set, Part 1 Study 311

Characteristic	2 Prior Doses Group A Monovalent (Omicron BA.1) N=61	2 Prior Doses Group B Original Monovalent N=61	3 Prior Doses Group C Monovalent (Omicron BA.1) N=286	3 Prior Doses Group D Original Monovalent N=274	3 Prior Doses Group E Bivalent (Original and BA.1) 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 Monovalent (Omicron BA.1) N=61	2 Prior Doses Group B Original Monovalent N=61	3 Prior Doses Group C Monovalent (Omicron BA.1) N=286	3 Prior Doses Group D Original Monovalent N=274	3 Prior Doses Group E Bivalent (Original and BA.1) 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)

Characteristic	2 Prior Doses Group A Monovalent (Omicron BA.1) N=61	2 Prior Doses Group B Original Monovalent N=61	3 Prior Doses Group C Monovalent (Omicron BA.1) N=286	3 Prior Doses Group D Original Monovalent N=274	3 Prior Doses Group E Bivalent (Original and BA.1) N=269	Total N=951
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
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)

Source: Table 16 in Study 311 Part 1 Final CSR, BLA 125817 p. 77
Abbreviations: anti-N=anti-nucleocapsid; BMI=body mass index; COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction; SD=standard deviation; N= safety analysis set.
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.

Demographic characteristics were balanced across the 5 vaccine groups. Although participants were younger in Groups A and B (median age 31.1 to 38.0 years) than in Groups C, D, and E (median age 41.0 to 42.0 years), the majority of participants in all 5 groups were female (52.2% to 63.9%), White (77.0% to 81.8%), and of Australian ethnicity (82.0% to 88.1%).

The median time between the previous dose of COVID-19 vaccine and the dose of study vaccine was approximately 6 months (177 to 182 days) for Groups C, D, and E with a history of 3 prior mRNA COVID-19 vaccine doses, and approximately 9 months (265 to 266 days) for Groups A and B with a history of 2 prior mRNA COVID-19 doses.

> *Clinical Reviewer Comment: There are notable demographic differences between the participants with 2 prior mRNA COVID-19 doses (Groups A and B) and those with 3 prior mRNA COVID-19 vaccines (Groups C, D, and E). The younger median age and the slightly higher percentage of female participants among those with 2 prior doses would not be expected to have a significant impact on immune responses compared with those previously vaccinated with 3 doses. However, the longer interval of time between the most recent mRNA COVID-19 vaccine and the study vaccine (approximately 9 months in the groups with 2 prior doses versus 6 months in the groups with 3 prior doses) would be expected to impact the degree of neutralizing antibody waning prior to administration of study vaccine. The higher percentage of participants with serologic evidence of prior SARS-CoV-2 natural infection in the groups with 2 prior doses (70.5% to 72.1% with anti-N positivity at baseline) compared with the groups with 3 prior doses (50.9% to 52.9% with anti-N positivity at baseline) may reflect the longer interval between doses and possible waning of neutralizing antibodies. Since the primary immunogenicity population includes only Groups C, D, and E with 3 prior mRNA COVID-19 vaccine doses, and demographic characteristics are well balanced among these 3 groups, demographic differences related to the number of prior vaccine doses would not impact the primary immunogenicity analysis.*

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All participants enrolled in the study were medically stable with no autoimmune or immunodeficiency conditions requiring immunomodulatory therapy.

6.3.10.1.3 Participant Disposition

The disposition of study participants is presented in the table below.

Table 84. Participant Disposition, All Screened Participants, Part 1 Study 311

Disposition	2 Prior Doses Group A Monovalent (Omicron BA.1) n (%)	2 Prior Doses Group B Original Monovalent n (%)	3 Prior Doses Group C Monovalent (Omicron BA.1) n (%)	3 Prior Doses Group D Original Monovalent n (%)	3 Prior Doses Group E Bivalent (Original and Omicron BA.1) n (%)	Total n (%)
Total number of participants	--	--	--	--	--	--
Randomized	61 (100)	61 (100)	279 (100)	274 (100)	278 (100)	953 (100)
Completed	48 (78.7)	49 (80.3)	216 (77.4)	209 (76.3)	204 (73.4)	726 (76.2)
Discontinued	13 (21.3)	12 (19.7)	63 (22.6)	65 (23.7)	74 (26.6)	227 (23.8)
Primary reason for discontinuation	--	--	--	--	--	--
Withdrawal by participant	6 (9.8)	8 (13.1)	34 (12.2)	34 (12.4)	40 (14.4)	122 (12.8)
No longer interested in participating	4 (6.6)	3 (4.9)	4 (1.4)	4 (1.5)	7 (2.5)	22 (2.3)
Schedule doesn't allow for participation	2 (3.3)	4 (6.6)	22 (7.9)	27 (9.9)	25 (9.0)	80 (8.4)
Doesn't want to continue in safety follow-up	0	0	2 (0.7)	0	4 (1.4)	6 (0.6)
Other	0	1 (1.6)	5 (1.8)	1 (0.4)	1 (0.4)	8 (0.8)
Relocation	0	0	1 (0.4)	2 (0.7)	3 (1.1)	6 (0.6)
Lost to follow-up	7 (11.5)	4 (6.6)	28 (10.0)	30 (10.9)	34 (12.2)	103 (10.8)
Adverse event	0	0	0	1 (0.4)	0	1 (0.1)
Other	0	0	1 (0.4)	0	0	1 (0.1)

Source: T14.1.1, Adapted from Table 10 in Study 311 Part 1 Final CSR, BLA 125817, p. 60
Note: Data are presented as number and percentage (n [%]) of participants.

Of the 953 participants randomized to the 5 vaccine groups, 726 (76.2%) completed the study and 227 (23.8%) discontinued participation as of the study completion date of June 28, 2023. The most common reason for study discontinuation was participant decision to withdraw (122; 12.8%) followed by lost to follow-up (103; 10.8%). One participant assigned to receive the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in Group D withdrew due to an adverse event involving acute psychosis, which was assessed to be unrelated to the study vaccine (see narrative for participant). One participant assigned to receive the monovalent vaccine (Omicron BA.1) in Group C discontinued study participation for a reason listed as "other."

The safety analysis set, which was comprised of 951 randomized participants who received at least 1 dose of study vaccine, included:

- 61 in Group A who received monovalent vaccine (Omicron BA.1)
- 61 in Group B who received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
- 286 in Group C who received monovalent vaccine (Omicron BA.1)
- 274 in Group D who received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent),
- 269 in Group E who received bivalent vaccine (Original and Omicron BA.1)

Clinical Reviewer Comment: The overall discontinuation rate of 23.8%, was largely attributable to participant withdrawal due to schedule conflicts precluding study participation and lost to follow-up. This discontinuation percentage would not be expected to substantively impact immunogenicity results, as rates of discontinuation and the reasons for participant withdrawal were balanced across the 3 vaccine groups (Group C, D, and E) included in the per-protocol analyses of the study's primary immunogenicity endpoints.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The following two tables present the pre-specified co-primary endpoints and success criteria for neutralizing antibody GMT and SRR responses against the Omicron BA.1 sublineage induced by the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for the PP Analysis Set on Day 14 postvaccination.

Table 85. Serum Neutralizing Antibody Titers Against the Omicron BA.1 Subvariant Virus at Day 14 Following Booster Vaccination With Monovalent (Omicron BA.1), Novavax Covid-19 Vaccine, Adjuvanted (Original Monovalent), or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With Original Monovalent mRNA COVID-19 Vaccine, PP Neutralization Assay Analysis Subset, Part 1 Study 311

Parameter	Group C Monovalent (Omicron BA.1)	Group D Original Monovalent	Group E Bivalent (Original and BA.1)
Day 0 (baseline)[a]	--	--	--
n1	126	119	118
Median	20	20.0	20.0
Minimum–maximum	10-320	10-1280	10-320
GMT (MN_{50})	25.2	27.9	26.7
95% CI[b]	21.5, 29.5	22.9, 33.9	22.3, 31.8

Parameter	Group C Monovalent (Omicron BA.1)	Group D Original Monovalent	Group E Bivalent (Original and BA.1)
Day 14	--	--	--
n1	124	116	116
Median	160	80.0	80.0
Minimum–maximum	10-1280	10-1280	10-1280
GMT (MN_{50})	130.8	83.9	95.1
95% CI[b]	109.2, 156.7	69.6, 101.2	79.0, 114.5
n2	124	116	116
GMFR referencing Day 0	5.2	3.0	3.6
95% CI[b]	4.4, 6.1	2.6, 3.6	3.1, 4.3
SRR ≥4-fold increase,[c] n3/n2 (%)	91/124 (73.4)	59/116 (50.9)	75/116 (64.7)
95% CI[d]	64.7, 80.9	41.4, 60.3	55.2, 73.3

Source: Adapted from Study 311 Part 1 Final Clinical Study Report, Table 20 and eSub 3 CSR Addendum to Study 311 Part 1, Table 14.2.1.1.1.s
Abbreviations: CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; LLOQ=lower limit of quantitation; MN_{50}=microneutralization assay at an inhibitory concentration of 50%; N=number of participants in the assay-specific per-protocol (PP) Neutralization Assay Analysis Subset; n1=number of participants in the assay-specific PP Neutralization Assay Analysis Subset within each visit with non-missing data; n2=number of participants in the assay-specific PP Neutralization Assay Analysis Subset with non-missing data at both visits of interest; n3=number of participants who reported ≥4-fold increase with percentages calculated based on n2 as the denominator; SRR=seroresponse rate
a. Baseline was defined as the last non-missing assessment prior to booster vaccination.
b. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.
c. The SRR was defined as percentage of participants at the postvaccination visit with a titer ≥4-fold rise in MN50 level.
d. The 95% CI for percentage difference in SRRs was calculated using the exact Clopper-Pearson method.
Note: Values less than LLOQ were replaced by 0.5 × LLOQ

Table 86. Comparison of Serum Neutralizing Antibody Titers on Day 14 Following Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With Original Monovalent mRNA COVID-19 Vaccine, PP Neutralization Assay Analysis Subset, Part 1 Study 311

Comparison Between Groups	Monovalent (Omicron BA.1) vs Original Monovalent n=124	Bivalent (Original and Omicron BA.1) vs Original Monovalent n=116	Bivalent (Original and Omicron BA.1) vs Monovalent (Omicron BA.1) n=116
GMTR[a]	1.6	1.2	0.7
95% CI[a]	1.33, 2.03	0.95, 1.45	0.57, 0.88
Difference in SRR[b]	22.5	13.8	-8.7
95% CI[b]	10.3, 34.2	1.1, 26.1	-20.3, 3.0

Source: Adapted from Study 311 Part 1 Final Clinical Study Report, Table 20 and eSub 3 CSR Addendum to Study 311 Part 1
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups; MN_{50}=microneutralization assay at an inhibitory concentration of 50%; LLOQ=lower limit of quantitation; PP=Per-Protocol; PP-IMM=Per-Protocol Immunogenicity; SRR=seroresponse rate
a. An ANCOVA with vaccine group as fixed effect and baseline value as covariate was performed to estimate the GMTR. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of MN_{50} GMTs and the corresponding 95% CIs.
b. 95% CI for the percentage difference in SRRs was calculated based on the method of Miettinen and Nurminen.
Note: Values less than LLOQ were replaced by 0.5 × LLOQ

Monovalent Vaccine (Omicron BA.1) Immunogenicity Endpoints and Analyses at Day 14

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.6 with 95% confidence intervals: 1.33, 2.03, which met the superiority criterion (i.e., the lower limit of the 95% CI around the GMTR was >1).

- The estimated percentage difference in SRRs between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 22.5% (95% CI: 10.3, 34.2), which met the noninferiority criterion (i.e., the lower limit of the 95% CI around the percentage difference in SRRs was >-5%).

Clinical Reviewer Comment: Immunogenicity analyses for Omicron BA.1 met success criteria for superiority when compared with the Original monovalent vaccine. These analyses were limited by the fact that participants who tested COVID-19 positive by serology testing were excluded; therefore, results may not be generalizable to the general population. Results for the larger, more heterogeneous PP2 Analysis Subset are presented in Section 6.3.11.3. Results for the bivalent immunogenicity data, which were analyzed as secondary endpoints, are discussed in Section 6.3.11.2.

6.3.11.2 Analyses of Secondary Endpoints

Sequential testing of secondary immunogenicity endpoints (Day 14 neutralizing antibody GMTs and SRR responses against the Omicron BA.1 sublineage) was conducted as prespecified based on the success of the co-primary immunogenicity analyses. The objective of this analysis was to evaluate the noninferiority of the bivalent vaccine (Original and Omicron BA.1) compared with monovalent vaccine (Omicron BA.1).

The PP Analysis Set immunogenicity results for the bivalent vaccine (Original and Omicron BA.1) compared with the monovalent vaccine (Omicron BA.1) on Day 14 postvaccination against the Omicron BA.1 sublineage were as follows:

Bivalent Vaccine (Original and Omicron BA.1) Analysis on Day 14

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.1) versus the monovalent vaccine (Omicron BA.1) was 0.7 with 95% CI: 0.57, 0.88, which did not meet the noninferiority criterion (i.e., the lower limit of the 95% CI around the GMTR (0.57) was not >0.67).
- The estimated percentage difference in SRRs of the bivalent vaccine (Original and Omicron BA.1) minus the monovalent vaccine (Omicron BA.1) was -8.7% with 95% CI: -20.3%, 3.0%, which did not meet the noninferiority criterion (i.e., the lower limit of the 95% CI around the percentage difference in SRRs (-8.7) was not >-5%).

The above immunogenicity results did not meet the prespecified success criteria for noninferiority of the bivalent vaccine (Original and Omicron BA.1) compared with the monovalent vaccine (Omicron BA.1).

Clinical Reviewer Comment: Based on the statistical analysis plan prespecified in the protocol, the study did not proceed with further statistical analyses comparing the bivalent vaccine (Original and Omicron BA.1) with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Lower immune responses induced by the bivalent vaccine compared with the monovalent vaccine (Omicron BA.1) may reflect a dose-related effect, as each antigen component in the bivalent vaccine (Original and Omicron BA.1) was half of the dose contained in the Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) and in the monovalent vaccine (Omicron BA.1). In addition, these bivalent immunogenicity data from the PP Analysis Set are limited by the fact that subjects who tested positive at baseline for past SARS-CoV-2 infection by anti-N serology testing were excluded, and results may not be generalizable to the overall population. Descriptive data from the more representative PP2 Analysis Set, which did not exclude participants with serologic evidence of prior SARS-

CoV-2 infection and which demonstrated higher neutralizing antibody titers induced by the bivalent vaccine (Original and Omicron BA.1) on both Day 14 and 28 postvaccination, are presented below in Section 6.3.11.3.

The duration of neutralizing antibody responses generated by the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.1) were evaluated against the Omicron BA.1 sublineage over time as a secondary endpoint analysis:

- Baseline (Day 0) GMTs against the Omicron BA.1 sublineage were 25.2 (95% CI: 21.5, 29.5), 27.9 (95% CI: 22.9, 33.9), 26.7 (95% CI: 22.3, 31.8) for the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.1), respectively.
- At Day 28, GMTs against the Omicron BA.1 sublineage increased 4.8-fold to 122.3 (95% CI: 101.0, 148.0) for monovalent vaccine (Omicron BA.1), 2.9-fold to 77.5 (95% CI: 63.1, 95.3) for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 3.3-fold to 85.9 (95% CI: 71.2, 103.6) for the bivalent vaccine (Original and Omicron BA.1). SRRs were 74.1% (95% CI: 65.2, 81.8), 47.3% (95% CI: 37.7, 57.0), and 53.7% (95% CI: 43.8, 63.3), respectively.
- By Day 240, GMTs and SRRs against the Omicron BA.1 sublineage were 92.8 (95% CI: 37.6, 229.2) for monovalent vaccine (Omicron BA.1), 133.0 (95% CI: 50.0, 353.8) for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 56.6 (95% CI: 17.7, 180.7) for the bivalent vaccine (Original and Omicron BA.1). SRRs were 35.7% (95% CI: 12.8, 64.9), 66.7% (95% CI: 38.4, 88.2), and 35.7% (95% CI: 12.8, 64.9), respectively.

Clinical Reviewer Comment: Immunogenicity results over time show that after the rise in neutralizing antibody GMTs at Day 28 for all 3 study vaccines, the antibody titers induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) continued to rise at the 8-month timepoint while those induced by the monovalent vaccine (Omicron BA.1) and bivalent vaccine had waned by 8 months.

6.3.11.3 Subpopulation Analyses

Immunogenicity results were evaluated by the number and combination of prior COVID-19 vaccines received (i.e., Pfizer and/or Moderna) and by SARS-CoV-2 anti-N positivity at baseline.

Subgroup Analysis by Prior mRNA COVID-19 Vaccine:

Out of the 951 study participants who received a dose of study vaccine, 77.8% had received 3 prior doses of a Pfizer mRNA COVID-19 vaccine, 20.5% had received a mixed combination of prior Pfizer and Moderna mRNA COVID-19 vaccine doses, and 1.7% received 3 prior doses of a Moderna mRNA COVID-19 vaccine. There were too few participants in the study population who received the Moderna mRNA COVID-19 vaccine to draw conclusions about neutralizing antibody responses against the Omicron BA.1 sublineage by previous mRNA COVID-19 vaccine received.

Subgroup Analysis by Anti-N Positivity:

In conducting subgroup analysis by SARS-CoV-2 anti-N positivity at baseline, descriptive analyses of neutralizing antibody GMTs and SRRs were performed in the PP2 Neutralization Assay Subset (hereafter referred to as the PP2 subset), which did not exclude the 420 participants (50.5% of all those randomized to Groups C, D, and E) with positive SARS-CoV-2

serology at baseline. This subset was more heterogeneous and likely more representative of the indicated population than the PP Analysis Set.

PP2 Subset Monovalent and Bivalent Vaccine Antibody Responses Against the Omicron BA.1 Sublineage

The following two tables present the immunogenicity results for the PP2 Analysis Subset based on neutralizing antibody responses against the Omicron BA.1 sublineage induced by the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and BA.1) 14 and 28 days after study vaccination.

Table 87. Serum Neutralizing Antibody Titers Against the Omicron BA.1 Virus Following Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With Original Monovalent COVID-19 Vaccine, PP Neutralization Assay Analysis Subset 2, Part 1 Study 311

Parameter	Group C Monovalent (Omicron BA.1)	Group D Original Monovalent	Group E Bivalent (Original and BA.1)
Day 0 (baseline)[a]	--	--	--
n1	258	251	240
Median	160.0	160.0	160.0
Minimum-maximum	10-2560	10-2560	10-10240
GMT (MN_{50})	98.1	106.0	105.0
95% CI[b]	80.4, 119.7	86.6, 129.8	85.1, 129.5
Day 14	--	--	--
n1	250	245	235
Median	320.0	320.0	320.0
Minimum-maximum	10-5120	10-2560	10-5120
GMT (MN_{50})	316.5	217.8	246.1
95% CI[b]	268.2, 373.4	185.9, 255.2	207.3, 292.2
n2	250	245	235
GMFR referencing Day 0	3.3	2.1	2.4
95% CI[b]	2.9, 3.7	1.8, 2.3	2.1, 2.7
SRR ≥4-fold increase[c], n3/n2 (%)	135/250 (54.0)	78/245 (31.8)	96/235 (40.9)
95% CI[d]	47.6, 60.3	26.1, 38.1	34.5, 47.4
Day 28	--	--	--
n1	241	235	221
Median	320.0	160.0	160.0
Minimum-maximum	10-5120	10-2560	10-10240
GMT (MN_{50})	283.6	195.5	211.5
95% CI[b]	240.7, 334.1	165.6, 230.8	177.4, 252.2
n2	241	235	221
GMFR referencing Day 0	2.8	1.9	2.0
95% CI[b]	2.5, 3.2	1.6, 2.1	1.8, 2.2
Percentage SRR ≥4-fold increase[c], n3/n2 (%)	126/241 (52.3)	65/235 (27.7)	74/221 (33.5)
95% CI[d]	45.8, 58.7	22.0, 33.9	27.3, 40.1

Source: T14.2.1.1.3.s from eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups; MN50=microneutralization assay at an inhibitory concentration of 50%; N=number of participants in the assay-specific per-protocol 2 (PP2) Analysis Set; n1=number of participants in the assay-specific PP2 Analysis Set within each visit with non-missing data; n2=number of participants in the assay-specific PP2 Analysis Set with non-missing data

at both visits of interest; n3=number of participants who reported ≥4-fold increase with percentages calculated based on n2 as the denominator; LLOQ=lower limit of quantitation; PP=Per-Protocol; SRR=seroresponse rate.
a. Baseline was defined as the last non-missing assessment prior to booster vaccination.
b. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.
c. The SRR was defined as percentage of participants at each postvaccination visit with a titer ≥4-fold rise in MN50 level.
d. The 95% CI for percentage difference in SRRs was calculated using the exact Clopper-Pearson method.
Note: Values less than LLOQ were replaced by 0.5 × LLOQ

Table 88. Comparison of Serum Neutralizing Antibody Titers Against the Omicron BA.1 Virus Following Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With Original Monovalent COVID-19 Vaccine, PP Neutralization Assay Analysis Subset 2, Part 1 Study 311

Comparison Between Groups	Monovalent (Omicron BA.1) vs Original Monovalent	Bivalent (Original and Omicron BA.1) vs Original Monovalent	Bivalent (Original and Omicron BA.1) vs Monovalent (Omicron BA.1)
Day 14	--	--	--
GMTR[a]	1.5	1.1	0.7
95% CI[a]	1.3, 1.8	1.0, 1.3	0.65, 0.85
Difference in SRR[b], %	22.2	9.0	-13.1
95% CI[b]	13.5, 30.5	0.4, 17.5	-21.8, -4.3
Day 28	--	--	--
GMTR[a]	1.5	1.1	0.7
95% CI[a]	1.3, 1.7	0.9, 1.2	0.6, 0.8
Difference in SRRs[b], %	24.6	5.8	-18.8
95% CI[b]	15.9, 32.9	-2.6, 14.3	-27.5, -9.8

Source: T14.2.1.1.3.s from eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups; MN_{50}=microneutralization assay at an inhibitory concentration of 50%; LLOQ=lower limit of quantitation; PP=Per-Protocol; PP-IMM=Per-Protocol Immunogenicity; SRR=seroresponse rate
a. An ANCOVA with vaccine group as fixed effect and baseline value as covariate was performed to estimate the GMTR. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of MN_{50} GMTs and the corresponding 95% CIs.
b. 95% CI for the percentage difference in SRRs was calculated based on the method of Miettinen and Nurminen.
Note: Values less than LLOQ were replaced by 0.5 × LLOQ

As shown in the table above, results for the monovalent vaccine (Omicron BA.1) against the Omicron BA.1 virus in the PP2 Analysis Subset on Day 14 and Day 28 postvaccination were as follows:

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis on Day 14

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.5 (95% CI: 1.34, 1.76) (the lower limit of the 95% CI around the GMTR is >1).
- The estimated percentage difference in SRRs between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 22.2% (95% CI: 13.5, 30.5) (the lower limit of the 95% CI around the percentage difference in SRRs is >-5%).

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis on Day 28

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.5 (95% CI: 1.28, 1.72) (the lower limit of the 95% CI around the GMTR is >1).

The estimated percentage difference in SRRs between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 24.6% (95% CI: 15.9, 32.9) (the lower limit of the 95% CI around the difference in SRRs is >-5%).

> *Clinical Reviewer Comment: The above immunogenicity results for the monovalent vaccine (Omicron BA.1) in the PP2 Analysis Subset, which included participants with serologic evidence of past SARS-CoV-2 infection, are likely to be more representative of the heterogeneity of the indicated population than the PP Analysis Set. Overall, these descriptive analyses meet the lower bound of the 95% CIs for both GMT and SRR at both Day 14 and 28 postvaccination and are supportive of the effectiveness of a single dose of monovalent vaccine (Omicron BA.1) against the Omicron BA.1 sublineage.*

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis on Day 14

Comparing the bivalent vaccine (Original and Omicron BA.1) with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron BA.1 sublineage showed the following results, which met the lower limits of the 95% confidence intervals for both the GMT ratio and the percentage difference in SRRs:

- Estimated GMTR 1.1 (95% CI: 1.00, 1.30) (the lower limit of the 95% CI around the GMTR >1).
- Estimated percentage difference in SRRs 9.0% (95% CI: 0.4, 17.5) (the lower limit of the 95% CI around the difference in SRRs is >-5%).

Comparing the bivalent vaccine (Original and Omicron BA.1) with the monovalent vaccine (Omicron BA.1) against the Omicron BA.1 sublineage showed the following results, which did not meet the lower limits of the 95% confidence intervals for both GMTR and the percentage difference in SRRs on Day 14:

- Estimated GMTR 0.7 (95% CI: 0.65, 0.85) (the lower limit of the 95% CI around the GMTR is not >1).
- Estimated percentage difference in SRRs -13.1% (95% CI: -21.8, -4.3) (the lower limit of the 95% CI around the difference in SRRs is not >-5%).

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis on Day 28

Comparing the bivalent vaccine (Original and Omicron BA.1) with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against the Omicron BA.1 sublineage showed the following, which did not meet the lower limits of the 95% confidence intervals for either the GMT ratio or the percentage difference in SRRs:

- Estimated GMTR 1.1 (95% CI: 0.93, 1.24) (the lower limit of the 95% CI around the GMTR is not >1).
- Estimated percentage difference in SRRs 5.8 (95% CI: -2.9, 14.3) (the lower limit of the 95% CI around the difference in SRRs is >-5%).

Comparing the bivalent vaccine (Original and Omicron BA.1) with the monovalent vaccine (Omicron BA.1) against the Omicron BA.1 sublineage showed the following, which did not met the lower limits of the 95% confidence intervals for both GMTR and the percentage difference in SRRs on Day 28:

- Estimated GMTR 0.7 (95% CI: 0.63, 0.83) (the lower limit of the 95% CI around the GMTR is not >1).

- Estimated percentage difference in SRRs -18.8% (95% CI: -27.5, -9.8) (the lower limit of the 95% CI around the difference in SRRs is not >-5%).

Clinical Reviewer Comment: The above descriptive immunogenicity analyses of the bivalent vaccine (Original and Omicron BA.1) against the Omicron BA.1 sublineage in the PP2 subset show mixed findings. When comparing the bivalent vaccine (Original and Omicron BA.1) with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron BA.1 sublineage, both vaccines generated comparable neutralizing antibody responses based on GMTs and SRRs on Day 14. However, on Day 28, the GMT ratio did not meet the >1 lower limit of the 95% CI (lower limit of the 95% CI 0.93) that would have been necessary to demonstrate superiority of the bivalent vaccine compared with the Original monovalent vaccine. This may be due to a dose-related effect, as each antigen component in the bivalent vaccine (Original and Omicron BA.1) was half of the dose contained in the Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) and in the monovalent vaccine (Omicron BA.1).

When compared with the monovalent vaccine (Omicron BA.1), the bivalent vaccine did not meet the lower bound of the 95% CI for GMT on Day 14 or for both GMT and SRR on Day 28 that would have been necessary to demonstrate noninferiority with the monovalent vaccine (BA.1). While the bivalent vaccine did not demonstrate either pre-specified superiority nor descriptive noninferiority to the monovalent (Omicron BA.1) vaccine (see Section 6.3.11.2), it came closest to inducing a noninferior immune response compared with the monovalent vaccine (BA.1) on Day 14 (estimated GMTR lower limit of the 95% CI of 0.65, which is a "near miss" from the 0.67 lower limit) in the larger, more serologically representative PP2 Analysis Set (n=240) versus the PP Analysis Set (n=116) (see Table 90). These bivalent vaccine results, on their own, would not be sufficient to support the effectiveness of a bivalent vaccine were one to be recommended in the future. Possible explanations for the inability of the bivalent data to demonstrate noninferiority compared with the monovalent vaccine include immunologic interference, physicochemical interactions between the two vaccine components, and/or antigen dose differences.

PP2 Subset Monovalent Vaccine (Omicron BA.1) and Bivalent Vaccine (Original monovalent and Omicron BA.1) Responses Against Ancestral (Wuhan) Strain

The table below summarizes the immunogenicity results for the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) pseudovirus on Day 14 and Day 28 in the PP2 subset.

Table 89. Serum Neutralizing Antibody Titers Against the Pseudovirus Expressing the Spike Protein From Ancestral (Wuhan) Strain Following Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With COVID-19 mRNA Vaccines, PP Neutralization Assay Analysis Subset 2, Part 1 Study 311

Parameter	Group C Monovalent (Omicron BA.1) N=258	Group D Original Monovalent N=251	Group E Bivalent (Original and Omicron BA.1) N=240
Day 0 (baseline)[a]	--	--	--
n1	258	251	240
Median	1280.0	1280.0	1280.0
Minimum-maximum	20-40960	20-40960	40-81920
GMT (MN_{50})	1152.7	1272.9	1222.2
95% CI[b]	976.5, 1360.6	1072.6, 1510.8	1019.4, 1465.4
Day 14	--	--	--
n1	250	245	235
Median	2560.0	2560.0	2560.0
Minimum-maximum	80-40960	160-81920	80-163840
GMT (MN_{50})	2206.2	2702.0	2544.7
95% CI[b]	1910.0, 2548.4	2347.9, 3109.4	2194.5, 2950.9
n2	250	245	235
GMFR referencing Day 0	1.9	2.1	2.1
95% CI[b]	1.8, 2.1	1.9, 2.4	1.9, 2.3
SRR ≥4-fold increase,[c] (%) (n3/n2)	32.0% (79/247)	32.8% (80/244)	35.8% (83/232)
95% CI[d]	26.2, 38.2	26.9, 39.1	29.6, 42.3
Day 28	--	--	--
n1	238	234	215
Median	2560.0	2560.0	2560.0
Minimum-maximum	40-20480	80-40960	160-81920
GMT (MN_{50})	1918.8	2456.0	2144.0
95% CI[b]	1657.9, 2220.6	2145.2, 2811.8	1842.3, 2495.2
n2	238	234	215
GMFR referencing Day 0	1.6	1.9	1.7
95% CI[b]	1.5, 1.8	1.7, 2.2	1.5, 1.9
SRR ≥4-fold increase,[c] %, (n3/n2)	23.5% (56/238)	29.1% (68/234)	27.4% (59/215)
95% CI[d]	18.3, 29.4	23.3, 35.3	21.6, 33.9

Source: T 14.2.1.2.3.s from eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR
Abbreviations: CI=confidence interval; GMTR=geometric mean titer ratio; N=number of participants in the assay-specific Analysis Set; n1=Number of participants in the assay-specific Analysis Set within each visit with non-missing data; n2=Number of participants in the assay-specific Analysis Set with non-missing data at both Day 0 and Day 28; n3=Number of participants achieving seroresponse; SRR=seroresponse rate
a. Baseline was defined as the last non-missing assessment prior to booster vaccination.
b. The 95% CI for GMT and GMFR were calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.
c. The SRR was defined as percentage of participants at each postvaccination visit with a titer ≥4-fold rise in MN_{50} level.
d. The 95% CI for the percentage difference in SRRs was calculated using the exact Clopper-Pearson method.

Table 90. Descriptive Comparison of Serum Neutralizing Antibody Titers Against the Pseudovirus Expressing the Spike Protein from Ancestral (Wuhan) Strain Following Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations with COVID-19 mRNA Vaccines, PP Neutralization Assay Analysis Subset 2, Part 1 Study 311

Comparison Between Groups	Monovalent (Omicron BA.1) vs Original Monovalent	Bivalent (Original and Omicron BA.1) vs Original Monovalent	Bivalent (Original and Omicron BA.1) vs Monovalent (Omicron BA.1)
Day 14	--	--	--
GMTR[a]	0.9	1.0	1.1
95% CI[a]	0.8, 1.0	0.9, 1.1	0.98, 1.3
Difference in SRRs[b], %	-1.1	3.1	4.1
95% CI[b]	-9.3, 7.2	-5.4, 11.6	-4.3, 12.5
Day 28	--	--	--
GMTR[a]	0.8	0.9	1.1
95% CI[a]	0.7, 0.9	0.77, 0.99	0.9, 1.2
Difference in SRRs[b], %	-5.7	-1.8	3.9
95% CI[b]	-13.6, 2.2	-10.0, 6.5	-4.0, 11.9

Source: T 14.2.1.2.3.s from eSub 3 CSR Addendum to the 2019nCoV-311 Part 1 CSR
Abbreviations: CI=confidence interval; GMTR=geometric mean titer ratio; SRR=seroresponse rate
a. An ANCOVA with vaccine group as fixed effect and baseline value as covariate was performed to estimate the GMTR. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of GMEUs and the corresponding 95% CIs.
b. 95% CI for the percentage difference in SRR was calculated based on the method of Miettinen and Nurminen.

As shown in the table above, the PP2 subset descriptive results after vaccination with the monovalent vaccine (Omicron BA.1) against the ancestral (Wuhan) strain were mixed as follows:

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis on Day 14

- Estimated GMTR 0.9 (95% CI: 0.7, 1.0) (the lower limit of the 95% CI around the GMTR was >0.67).
- Estimated percentage difference in SRRs -1.1% (95% CI: -9.3, 7.2) (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis on Day 28

- Estimated GMTR 0.8 (95% CI: 0.7, 0.9) (the lower limit of the 95% CI around the GMTR was >0.67).
- Estimated percentage difference in SRRs 5.7% (95% CI: -13.6, 2.2) (the lower limit of the 95% CI around the percentage difference in SRRs was not >-10%).

Clinical Reviewer Comment: The above descriptive immunogenicity analyses of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain show that both vaccines induce comparable neutralizing antibody responses based on the GMT ratio. The percentage difference in SRRs met the >-10% lower limit of the 95% confidence interval on Day 14 (lower limit of the 95% CI -9.3%) but missed this lower limit on Day 28 (lower limit of 95% CI -13.6%). Given the continued evolution of the SARS-CoV-2 virus, this analysis may no longer be clinically relevant.

Bivalent vaccine (Original and Omicron BA.1) against Ancestral (Wuhan) strain

As shown in Table 90, the descriptive results on Day 14 and Day 28 after vaccination against the ancestral (Wuhan) strain were the following for the PP2 subset:

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis on Day 14

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.0 (95% CI: 0.85, 1.09) (the lower limit of the 95% CI around the GMTR was >0.67).
- The estimated percentage difference in SRRs of the bivalent vaccine (Original and Omicron BA.1) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 3.1% (95% CI: -5.4, 11.6) (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis on Day 28

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 0.9 (95% CI: 0.77, 0.99) (the lower limit of the 95% CI around the GMTR was >0.67).
- The estimated percentage difference in SRRs between the bivalent vaccine (Original and Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was -1.8% (95% CI: -10.0, 6.5) (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

Clinical Reviewer Comment: The above immunogenicity analyses show that the bivalent vaccine (Original and Omicron BA.1) and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) induce comparable GMT and SRR neutralizing antibody responses against the ancestral (Wuhan) strain on Day 14 and Day 28 postvaccination. These data, while subject to the limitations of descriptive analysis, provide limited support for the effectiveness of a single dose of the bivalent vaccine technology against the ancestral (Wuhan) strain in adults with prior mRNA COVID-19 vaccination. Please see Section 6.4.11.1 for discussion of additional bivalent vaccine data submitted in this BLA.

6.3.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.3.10 for a summary of participant discontinuation.

6.3.11.5 Exploratory and Post Hoc Analyses

Neutralizing antibody responses induced by each of the 3 study vaccines over time were evaluated as an exploratory endpoint against the Omicron BA.4/5 sublineage for the PP Analysis Set (which excluded participants with anti-N positivity at baseline):

- Baseline (Day 0) GMTs against the Omicron BA.5 sublineage for the PP Analysis Set were 24.4 (95% CI: 20.6, 28.8) , 28.0 (95% CI: 23.2, 33.9), and 25.9 (95% CI: 21.9, 30.6) for monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.1), respectively.
- At Day 28, GMTs against the Omicron BA.5 sublineage increased 3.1-fold to 75.4 (95% CI: 61.4, 92.4) for the monovalent vaccine (Omicron BA.1), 2.7-fold to 71.4 (95% CI: 56.8, 89.7) for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 2.8-fold to 73.1 (95% CI: 60.2, 88.8) for the bivalent vaccine. SRRs were 50.0% (95% CI: 40.6, 59.4), 41.8% (95% CI: 32.5, 51.6), and 50.9% (95% CI: 41.1, 60.7), respectively.
- At Day 240, GMTs against the Omicron BA.5 sublineage were 80.0 (95% CI: 24.7,

259.0) for monovalent vaccine (Omicron BA.1), 133.0 (95% CI: 49.5, 357.6) for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 42.0 (95% CI:13.6, 129.6) for the bivalent vaccine (Original and Omicron BA.1). SRRs were 42.9% (95% CI:17.1, 71.1), 73.3% (95% CI: 44.9, 92.2), and 35.7% (95% CI:12.8, 64.9), respectively.

Neutralizing antibody response against the Omicron BA.5 sublineage for the PP2 Analysis Subset (which included participants with anti-N positivity at baseline) showed:

- Baseline (Day 0) GMTs against the Omicron BA.5 sublineage for the PP Analysis Set were 92.7 (95% CI: 75.8, 113.5), 103.1(95% CI: 84.5, 126.0), and 101.7(95% CI: 82.0, 126.0) for monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.1), respectively.
- At Day 28, GMTs against the Omicron BA.5 sublineage increased 2.0-fold to 196.2 (95% CI: 164.3, 234.5) for the monovalent vaccine (Omicron BA.1), 1.7-fold to 172.2 (95% CI: 145.2, 204.3) Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 1.7-fold to 180.3 (95% CI: 150.5, 215.9) for the bivalent vaccine. SRRs were 32.8% (95% CI: 26.9, 39.1), 24.7% (95% CI: 19.3, 30.7), and 29.0% (95% CI: 23.1, 35.4), respectively.
- At Day 240, GMTs against the Omicron BA.5 sublineage were 121.3 (95% CI: 62.0, 237.2) for monovalent vaccine (Omicron BA.1), 175.7.0 (95% CI: 111.7, 276.4) for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and 110.0 (95% CI: 59.5, 203.5) for the bivalent vaccine (Original and Omicron BA.1). SRRs were 28.0% (95% CI: 12.1, 49.4), 29.7% (95% CI: 15.9, 47.0), and 13.5% (95% CI: 4.5, 28.8), respectively.

Reviewer Comment: The increase in neutralizing antibody titers against the Omicron BA.5 sublineage after vaccination with the monovalent vaccine (Omicron BA.1) which persisted for 8 months after vaccination, demonstrates a level of cross-reactivity against another circulating Omicron-lineage virus. It is notable that in the PP2 Analysis Subset, which included participants with serologic evidence of past SARS-CoV-2 natural infection and prior vaccination (i.e., hybrid immunity), immune responses at each time point show consistently higher neutralizing antibody titers and lower rates of seroconversion than the respective immune responses in the PP Analysis Set, which included participants with prior vaccination but without a history of prior natural infection.

6.3.12 Safety Analyses

6.3.12.1 Methods

Please see Section 6.3.7.

6.3.12.2 Overview of Adverse Events

Study 311 Part 1 safety data included solicited local AEs, solicited systemic AEs, unsolicited AEs, treatment related unsolicited AEs, and a median of 244 days (8 months) of safety follow-up for MAAEs (treatment-related), SAEs, and AESIs.

The table below presents an overall summary of solicited and unsolicited AEs for all participants who had received 2 prior mRNA COVID-19 vaccines (Groups A and B) or 3 prior mRNA COVID-19 vaccines (Groups C, D, and E).

Table 91. Frequency and Percentage of Solicited and Unsolicited Treatment-Emergent Adverse Events After Booster Vaccination with Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Adult Participants Who Previously Received 3 Vaccinations with Prototype COVID-19 mRNA Vaccines, Safety Analysis Set, Part 1 Study 311

Adverse Event	Group A Monovalent (Omicron BA.1) N=61 n (%)	Group B Original Monovalent N=61 n (%)	Group C Monovalent (Omicron BA.1) N=286 n (%)	Group D Original Monovalent N=274 n (%)	Group E Bivalent (Original and Omicron BA.1) N=269 n (%)
Solicited local TEAEs[a, d]	47 (78.3)	42 (72.4)	196 (69.3)	193 (71.0)	173 (64.6)
Grade 3 or higher	1 (1.7)	1 (1.7)	5 (1.8)	1 (0.4)	3 (1.1)
Solicited systemic TEAEs[b, d]	32 (53.3)	34 (58.6)	176 (62.2)	158 (58.1)	166 (61.9)
Grade 3 or higher	3 (5.0)	2 (3.4)	21 (7.4)	10 (3.7)	8 (3.0)
Any unsolicited TEAE	18 (29.5)	19 (31.1)	92 (32.2)	105 (38.3)	90 (33.5)
Treatment-related	0	2 (3.3)	13 (4.5)	8 (2.9)	7 (2.6)
Severe	0	0	0	4 (1.5)	0
Treatment-related severe	0	0	0	0	0
Any unsolicited serious TEAE	1 (1.6)	2 (3.3)	8 (2.8)	4 (1.5)	4 (1.5)
Treatment-related	0	0	0	0	0
Any unsolicited TEAE leading to study discontinuation	0	0	0	1 (0.4)	0
Treatment-related	0	0	0	0	0
Any unsolicited treatment-emergent MAAE	2 (3.3)	3 (4.9)	14 (4.9)	18 (6.6)	11 (4.1)
Treatment-related	0	0	1 (0.3)	0	0
Treatment-related serious MAAE	0	0	0	0	0
Severe MAAE	0	0	0	3 (1.1)	0

Adverse Event	Group A Monovalent (Omicron BA.1) N=61 n (%)	Group B Original Monovalent N=61 n (%)	Group C Monovalent (Omicron BA.1) N=286 n (%)	Group D Original Monovalent N=274 n (%)	Group E Bivalent (Original and Omicron BA.1) N=269 n (%)
Related Severe MAAE	0	0	0	0	0
Any unsolicited AESI: PIMMC[c]	0	0	2 (0.7)	2 (0.7)	1 (0.4)
Treatment-related	0	0	0	0	0
Any unsolicited AESI: complications due to COVID-19	0	0	0	0	0
Any myocarditis/pericarditis	0	0	0	0	0

Source: Adapted from Study 311 Part 1 Final CSR, Table 59
Abbreviations: AESI=treatment-emergent adverse events of special interest; CRF=case report form; MAAE=medically attended adverse event; N=number of participants in the Safety Analysis Set; n=number of participants at each level of summarization with percentages based on the number of participants in the Safety Analysis Set within each treatment; PIMMC=potential immune-mediated medical conditions; TEAE=treatment-emergent adverse event.
a. Injection site reaction
b. Solicited local and systemic TEAEs were reported within 7 days (Days 0 to 6) after booster vaccination.
c. PIMMCs were recorded according to protocol-defined criteria and by the investigator reporting in the CRF.
d. Solicited adverse reaction percentages are reported based on the 60, 58, 283, 272, and 268 participants who completed eDiary solicited ARs in Group A, B, C, D, and E, respectively.
Note: If any solicited TEAE extended beyond 6 days after vaccination (toxicity grade ≥1), it was recorded as an TEAE with the start date the 7th day following the relevant study vaccination and followed to resolution. The solicited TEAEs that continued past Day 6 were not included in this summary. At each level of participant summarization, a participant was counted once if the participant reported one or more events.
Note: Relationship and severity are based on the data reported by site – i.e., missing information is not imputed.
Maximum toxicity grading is standardized according to the FDA toxicity grading scale: Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, and Grade 4=Potentially Life Threatening.
Note: Values are presented as n (%).
Note: Related MAAE, Serious TEAE, PIMMC, AESI (COVID 19), Myocarditis/Pericarditis, and TEAEs leading to any discontinuation are reported through end of study. Other TEAEs are reported through 28 days after study vaccination.

Clinical Reviewer Comment: Overall, the rates and severities of adverse events associated with the monovalent vaccine (Omicron BA.1) and bivalent vaccine (Original and Omicron BA.1) appear comparable to those associated with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Frequencies of solicited and unsolicited adverse events, both nonserious and serious, are analyzed below.

Solicited Adverse Reactions

The table below summarizes the solicited local injection site ARs reported by severity.

Table 92. Frequency and Percentage of Solicited Local Adverse Events for 7 Days After Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Participants Who Previously Received 3 Vaccinations With COVID-19 mRNA Vaccines, Safety Analysis Set, Part 1 Study 311

Adverse Event	Group A Monovalent (Omicron BA.1) N=60 n (%)	Group B Original Monovalent N=58 n (%)	Group C Monovalent (Omicron BA.1) N=283 n (%)	Group D Original Monovalent N=272 n (%)	Group E Bivalent (Original and Omicron BA.1) 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)
Grade 4	0	0	0	0	0
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)
Grade 4	0	0	0	0	0
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
Grade 4	0	0	0	0	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)
Grade 4	0	0	0	0	0
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)
Grade 4	0	0	0	0	0
Swelling	--	--	--	--	--
Any Grade	0	0	7 (2.5)	3 (1.1)	4 (1.5)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0

Source: Modified from Table 36 in the Study 311 Part 1 Interim Study Report, Table 61 in the study 311 Final CSR, and source T 14.3.2.1.1

Note: Table includes only those participants who completed eDiary solicited AEs.

Abbreviations: AE=adverse event

Notes: At each level of participant summarization, a participant was counted once for the most severe grade if the participant reported one or more reaction. Maximum toxicity grading is standardized according to the FDA toxicity grading scale: Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Potentially Life Threatening.

As shown in the previous table, percentages of local injection site ARs were relatively balanced across all vaccine groups, occurring with percentages ranging from 64.6% to 78.3%. Pain and tenderness were the most common injection site ARs reported (ranging from 64.6% to 78.3% of

participants in each group). Redness and swelling were reported in less than 3% of participants in any group. No Grade 4 events were reported.

The median day of onset was Day 1 or 2 for pain and tenderness, Day 1.5 or 2 for swelling, and Day 1, 2, or 3 for redness, with median durations of 2 days for pain/ tenderness, 1.0 to 2.0 days for swelling, and 1.0 to 3.0 days for redness.

> *Clinical Reviewer Comment: Local injection site ARs of pain and tenderness were common, affecting well over half of all participants in all vaccine groups (64.6% to 78.3%). Although the highest percentage of participants reporting injection site pain were in the monovalent vaccine (Omicron BA.1) group with 2 prior mRNA vaccines (55.0%) compared with all other groups (range 35.8% to 43.1% of participants), the percentage of pain and/or tenderness was similar across all vaccine groups. Overall, local injection site reactogenicity of the updated variant monovalent vaccine (Omicron BA.1) and bivalent vaccine (Original and Omicron BA.1) appears comparable to local injection site reactogenicity of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).*

The table below presents a summary of frequency and percentage of solicited systemic ARs by severity.

Table 93. Frequency and Percentage of Solicited Systemic Adverse Events for 7 Days After Booster Vaccination With Monovalent (Previously Received 3 Vaccinations With COVID-19 mRNA Vaccines), Safety Analysis Set, Part 1 Study 311

Adverse Event	Group A Monovalent (Omicron BA.1) N=60 n (%)	Group B Original Monovalent N=58 n (%)	Group C Monovalent (Omicron BA.1) N=283 n (%)	Group D Original Monovalent N=272 n (%)	Group E Bivalent (Original and Omicron BA.1) 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	0	0	1 (0.4)	0	0
Grade 4	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)
Grade 4	0	0	0	0	0
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)
Grade 4	0	0	0	0	0
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)
Grade 4	0	0	0	0	0

Adverse Event	Group A Monovalent (Omicron BA.1) N=60 n (%)	Group B Original Monovalent N=58 n (%)	Group C Monovalent (Omicron BA.1) N=283 n (%)	Group D Original Monovalent N=272 n (%)	Group E Bivalent (Original and Omicron BA.1) N=268 n (%)
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
Grade 4	0	0	0	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)
Grade 4	0	0	0	0	0
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
Grade 4	0	0	0	0	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)
Grade 4	0	0	0	0	0

Source: Table 62 in the Study 311 Part 1 Final CSR, and T14.3.2.1.1
Abbreviations: AE=adverse event; N=number of participants who received at least one dose and completed at least one day of vaccine reactogenicity diary.; n=number of participants at each level of summarization with percentages based on the number of participants in the Safety Analysis Set within each treatment
Note: Table includes only those participants who completed eDiary solicited AEs. Note: At each level of participant summarization, a participant was counted once for the most severe grade if the participant reported one or more reaction. Maximum toxicity grading is standardized according to the FDA toxicity grading scale.
a. Temperature ≥38°C.

As shown in the previous table, the percentages of participants reporting solicited systemic ARs were relatively balanced across all vaccine groups: 53.3% to 62.2% of monovalent vaccine (Omicron BA.1) recipients, 58.1% to 58.6% of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients, and 61.9% of bivalent vaccine (Original and Omicron BA.1) recipients. Fatigue/ malaise, headache, and muscle pain were the most frequent solicited systemic ARs. Fever was reported in less than 2% of participants in any vaccine group.

The median day of onset was Day 1 or 2 for most events, with a later median onset for nausea/vomiting (2.5 to 4 days), headache (2 to 4 days), joint pain (2 to 3.5 days) and fever (1 to 5 days). The median duration was 1 to 3 days for individual AR events.

Grade 3 or higher solicited systemic ARs were reported by 5.0% to 7.4% of participants in the monovalent vaccine (Omicron BA.1) groups, 3.4% to 3.7% of participants for the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) groups, and 3.0% of participants in the bivalent vaccine (Original and Omicron BA.1) group. One solicited systemic grade 4 AR of fever was reported by a participant with 3 prior mRNA COVID-19 vaccines in the monovalent vaccine (Omicron BA.1) group.

> *Clinical Reviewer Comment: Overall, the percentage and severity of local and systemic adverse reactions are similar between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and do not suggest new*

safety concerns regarding the reactogenicity of a single dose of updated monovalent vaccine in previously mRNA COVID-19 vaccinated individuals.

Subgroup analyses were conducted by sex, race, and ethnicity. Solicited ARs were reported at higher percentages in female (74.4% to 90.2%) than male (69.5% to 75.2%) participants across all vaccine groups. Higher percentages of solicited ARs were also reported in White participants across all vaccine groups (78.7% to 84.2%) than in Asian participants (55.6% to 78.4%) The subgroup analyses for other races were of limited value as there were too few participants of other races. Subgroup analyses by ethnicity were also limited as most participants were Australian (>85%), and there were too few participants of other ethnicities.

Clinical Reviewer Comment: Minor differences in reactogenicity were observed in subgroup analysis by sex, with a higher percentage of females experiencing solicited ARs than males. No other notable differences were observed among the demographic subgroups, as many race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Unsolicited AEs

Unsolicited AEs reported through 28 days postvaccination were balanced across all vaccine groups: 29.5% to 34.3% of monovalent vaccine (Omicron BA.1) recipients, 31.1% to 38.3% of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients, and 33.5% of the bivalent vaccine (Original and Omicron BA.1) recipients. Few participants reported severe unsolicited AEs: none, 4 (1.5%), and none in the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively. There were no severe treatment-related AEs.

Unsolicited AEs were most frequently reported in the MedDRA SOC of *Infections and Infestations,* with the highest percentage reported in 16 (26.2%) of participants with 2 prior mRNA COVID-19 vaccines in the monovalent vaccine (Omicron BA.1) group. Among the remaining groups, this SOC was reported by 11 (18.0%) of participants with 2 prior mRNA COVID-19 vaccines in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group and by 38 (13.3%), 47 (16.1%), and 60 (20.1%) participants with 3 prior mRNA COVID-19 vaccines in the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively.

Within this SOC, the most frequent AEs were upper respiratory tract infection and COVID-19 among all vaccine groups. Upper respiratory tract infection occurred in 11.5% and 6.6% of those with 2 prior mRNA COVID-19 vaccines who received monovalent vaccine (Omicron BA.1) or Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), respectively and in 3.5%, 5.1%, and 8.6%, for those with 3 prior vaccines who received monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively.

The occurrence of COVID-19 was relatively balanced in those with 2 prior mRNA COVID-19 vaccines who received monovalent vaccine (Omicron BA.1) and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (9.8% and 6.6%, respectively) and in those with 3 prior mRNA COVID-19 vaccines who received monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups (3.8%, 4.0%, and 6.7%, respectively).

Clinical Reviewer Comment: Overall percentages and severity of unsolicited AEs were similar between the monovalent vaccine (Omicron BA.1) recipients and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients. Among recipients of the monovalent vaccine (Omicron BA.1), it is notable that a slightly higher percentage of participants with 2 prior mRNA COVID-19 vaccines experienced upper respiratory infection and COVID-19 (11.5% and 9.8%, respectively) within 28 days of study vaccination than those with 3 prior mRNA COVID-19 vaccines (3.5% and 3.8%, respectively). Reasons for this are not entirely clear, but the longer time interval between the study vaccine and prior mRNA COVID-19 vaccine in those with 2 prior mRNA COVID-19 vaccines may have been a contributing factor.

Percentages of unsolicited AEs were generally similar across subgroups based on sex, race, ethnicity, and baseline SARS-CoV-2 status, though these analyses were limited by the low number of participants in several subgroups.

Medically Attended Adverse Events

Among all vaccine groups, MAAEs through 28 days after vaccination were most frequently reported in the MedDRA SOC of *Infections and* Infestations: 3.1% to 3.3% of monovalent vaccine (Omicron BA.1) recipients, 2.9% to 3.3% of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients, and 3.0% of bivalent vaccine (Original and Omicron BA.1) recipients. Within this SOC, infection with COVID-19 (ranging from 1.0% to 1.6%, 1.1% to 3.3%, and 0.4%, respectively) was the most frequent MAAE reported. Most MAAEs were mild or moderate in severity, with 3 (1.1%) Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients reporting severe MAAEs of anaphylactic reaction, urinary tract infection, and back pain. None of these severe MAAEs were considered related to study vaccine.

MAAEs through the end of study (8 months of safety follow-up) were reported in 90 participants (9.5%). Of these participants, 18 experienced MAAEs that were classified as serious (see SAE narrative summaries below). None of these serious MAAEs were considered related to study vaccine.

Treatment-related MAAEs were collected through the end of study. One (0.3%) participant who received the monovalent vaccine (Omicron BA.1) had a treatment-related MAAE (insomnia). This event, which was considered non-serious and mild in severity, had a start date of Day 2 and remained ongoing at the interim data cutoff date (72 days), with an outcome of recovering/resolving and no available follow-up information through the end of study.

Based on subgroup analyses, MAAEs were reported at similar percentages between male and female participants. Subgroup analyses by race and ethnicity were limited due to too few participants with MAAEs in these subgroups for meaningful comparisons. Subgroup analyses of severe MAAEs were of limited value as there were too few participants with severe events.

6.3.12.3 Deaths

There were no deaths in the study.

6.3.12.4 Nonfatal Serious Adverse Events

SAEs through the end of study were reported by 19 participants in groups A, B, C, D, and E: 9 participants receiving the monovalent vaccine (Omicron BA.1), 6 participants receiving the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and 4 participants receiving the

bivalent vaccine (Original and Omicron BA.1). None of the SAEs was considered related to vaccine by the investigator or Applicant. Brief details of each SAE are provided below.

1. A 39-year-old White male in the monovalent vaccine (Omicron BA.1) group experienced an SAE of appendicitis 57 days after receiving 1 dose of study vaccine.

2. A 46-year-old White female in the monovalent vaccine (Omicron BA.1) group experienced an SAE of breast cancer identified by mammogram 41 days after receiving 1 dose of study vaccine. She subsequently underwent bilateral mastectomy.

3. A 27-year-old White male in the monovalent vaccine (Omicron BA.1) group experienced an SAE of streptococcal pneumonia 192 days after receiving 1 dose of study vaccine.

4. A 60-year-old White male in the monovalent vaccine (Omicron BA.1) group experienced an SAE of right upper lobe pneumonia 175 days after receiving 1 dose of study vaccine. He was hospitalized, treated with oral antibiotics, and symptoms resolved.

5. A 34-year-old Asian female in the monovalent vaccine (Omicron BA.1) group experienced an SAE of papillary thyroid cancer, diagnosed following total thyroidectomy for a nodule, 146 days after receiving 1 dose of study vaccine.

6. A 28-year-old White female in the monovalent vaccine (Omicron BA.1) group with a history of depression, anxiety, and post-traumatic stress disorder experienced an SAE of substance-induced psychotic disorder following consumption of an unknown amount of cannabinoids 161 days after receiving 1 dose of study vaccine.

7. A 40-year-old White male in the monovalent vaccine (Omicron BA.1) group with a history of depression experienced an SAE of depression approximately 154 days postvaccination. The participant had a depression exacerbation and was admitted to the hospital and discharged the following day.

8. A 47-year-old White male in monovalent vaccine (Omicron BA.1) group with a history of enlarged thyroid experienced an SAE of follicular thyroid cancer diagnosed at the time of elective thyroidectomy surgery 100 days after receiving 1 dose of study vaccine.

9. A 23-year-old Asian female in the monovalent vaccine (Omicron BA.1) group with a history of dysmenorrhea experienced an SAE of dysmenorrhea with onset of symptoms 19 days postvaccination. The participant was hospitalized for pain management and symptoms resolved.

10. A 58-year-old White male in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group who experienced an SAE of methamphetamine intoxication 239 days after 1 dose of study vaccine.

11. A 27-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group who experienced an SAE of nail bed infection requiring incision, drainage, and IV antibiotics in the hospital 110 days after receiving 1 dose of study vaccine.

12. A 37-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with a history of endometriosis who experienced an SAE of

progression of endometriosis for which a planned laparoscopy was performed 50 days after receiving 1 dose of study vaccine.

13. A 58-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with a history of coronary artery disease, hypercholesterolemia, and BMI of 40.9 kg/m^2 who experienced an SAE of unstable angina 75 days after 1 dose of study vaccination. Onset of chest pain began on postoperative day 4 after a planned angiogram and stent placement, which prompted evaluation in the emergency department where troponin elevation was noted. The event resolved without intervention, and he was discharged from the hospital.

14. A 25-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with a history of anaphylaxis to nuts experienced an SAE of anaphylactic reaction after ingesting nuts approximately 11 days after 1 dose of study vaccine. She was evaluated and monitored in the emergency department before being discharged.

15. A 55-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group experienced an SAE of gastroenteritis approximately 46 days postvaccination, resolved.

16. A 25-year-old White female in the bivalent vaccine (Original and Omicron BA.1) group with a history of dysmenorrhea experienced an SAE of endometriosis diagnosed approximately 54 days postvaccination, resolved.

17. A 20-year-old White female in the bivalent vaccine (Original and Omicron BA.1) group experienced an SAE of pyelonephritis 211 days after receiving 1 dose of study vaccination, resolved.

18. A 53-year-old White male in the bivalent vaccine (Original and Omicron BA.1) group experienced SAEs of lower limb cellulitis and diabetic toe ulcer 51 days after 1 dose of study vaccine, resolved.

19. A 38-year-old White male in the bivalent vaccine (Original and Omicron BA.1) group experienced an SAE of ventricular extrasystole 212 days after receiving 1 dose of study vaccine, resolved.

Reviewer Comment: This reviewer agrees with the assessment that each of these reported SAEs are not related to the study vaccine based on lack of temporal association, biological implausibility, and/or alternative etiology in each case.

Subgroup analyses of SAEs by sex, race, and ethnicity were inconclusive as there were too few participants with serious events.

6.3.12.5 Adverse Events of Special Interest (AESI)

Five participants experienced AESIs, all of which were deemed not related to the study vaccine by the Investigator:

1. The SAE of anaphylactic reaction to ingested nuts in a participant who received the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group described above was also categorized as an AESI in the subcategory of Potential Immune-Mediated Medical Conditions (PIMMC).

2. A 53-year-old White female in the monovalent vaccine (Omicron BA.1) group experienced an AESI of Bell's palsy 209 days after receiving 1 dose of study vaccine. The participant was treated with oral prednisolone, and symptoms resolved.

3. A 27-year-old White male in the monovalent vaccine (Omicron BA.1) group experienced an AESI of peripheral neuropathy with onset of tingling, numbness, and pain symptoms 231 days after receiving 1 dose of study vaccine that was considered a possible side effect of moxifloxacin, which had been prescribed for pneumonia. The event was non-serious, was medically attended, and did not lead to study discontinuation.

4. A 49-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, with a history of ADHD and coeliac disease, experienced an AESI (PIMMC) of psoriatic arthropathy occurring on 2 occasions (25 days and 33 days) after receiving 1 dose of study vaccine. The event was non-serious, not medically attended, and did not lead to study discontinuation.

5. A 56-year-old White female in the bivalent vaccine (Original and Omicron BA.1) group with a history of recurrent urinary tract infections experienced an AESI of celiac disease after onset of abdominal pain and vomiting 8 days after receiving 1 dose of study vaccine prompted an emergency room evaluation, which resulted in the diagnosis of possible gastric ulcer. Ongoing symptoms and a subsequent colonoscopy/ gastroscopy led to the diagnosis of celiac disease 112 days after receiving the study vaccination. The event was considered nonserious and did not lead to study discontinuation.

Clinical Reviewer Comment: This reviewer agrees with the Investigator that these AESIs are unlikely to be related to the study vaccine based on a lack of temporal association or biological implausibility in 3 out of the 5 cases (anaphylactic reaction, Bell's palsy, peripheral neuropathy). In the remaining 2 cases, there is a close temporal relationship to the single-dose vaccine (within 25 days for onset of psoriatic arthropathy and within 8 days for onset of gastrointestinal symptoms later diagnosed as celiac disease), however there is questionable biological plausibility for relatedness, and the emergence of symptoms postvaccination is most likely related to the presence of undiagnosed conditions.

6.3.12.6 Clinical Test Results

All eligible female participants in Part 1 of the study had negative pregnancy tests prior to study vaccination.

6.3.12.7 Dropouts and/or Discontinuations

One participant experienced an AE leading to study vaccine discontinuation.

A 36-year-old male in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with a history of depression experienced the onset of acute psychosis on Day 19 postvaccination that resolved by Day 31. The condition was described as moderate in severity and deemed unrelated to the study vaccine. Upon request, additional follow up of this participant was received from Novavax, which included the participant's self-report of treatment-resistant depression and mild psychosis and initiation of treatment with olanzapine. The participant was lost to follow up, which resulted in the Investigator withdrawing the participant due to the reported adverse event. Following study discontinuation, follow-up was received noting the participant was under the care of his regular general practitioner and the psychotic episode resolved after starting olanzapine. The event was considered resolved.

6.3.13 Study Summary and Conclusions

Effectiveness

Study 311 Part 1 provides immunogenicity data supporting the effectiveness of a single-dose of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) against SARS-CoV2 variants in COVID-19 vaccine-experienced individuals 18 years of age and older, as demonstrated by superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

These superior neutralizing antibody responses can also be extrapolated to adolescents 12 through 17 years of age in the context of previously reviewed comparable efficacy and immunogenicity results between adult and adolescents observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and comparable immunogenicity results between a 2-dose series and a 1-dose "booster" of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adolescents (see Decision Memorandum).

Additional supportive immunogenicity data include descriptive noninferior neutralizing antibody responses (as measured by GMTR) induced by the monovalent (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain. Although the difference in SRR following administration of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain did not meet the expected lower bound of the 95% confidence interval on Day 28 based on descriptive analysis, the successful GMTR comparison is reassuring given the limitations of SRR comparisons.

The bivalent vaccine (Original and BA.1) did not show superiority compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.1 at the 28-day timepoint in descriptive analyses. This result may be due to a dose-related effect, as each antigen component in the bivalent vaccine (Original and Omicron BA.1) was half of the dose contained in the Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) and in the monovalent vaccine (Omicron BA.1). As the bivalent vaccine (Original and Omicron BA.5) induced a more robust immune response compared with the bivalent vaccine (Original and Omicron BA.1), a possible explanation for the difference in immunogenicity between these two bivalent vaccines may involve hybrid immunity of the study population exposed to each of these vaccines (see Section 6.4.11.1). At the time of Omicron BA.5 circulation as a variant of concern, a larger percentage of the population had been vaccinated and exposed to COVID-19 infection, thus increasing hybrid immunity leading to heightened immune responses within that population (Spinardi and Srinastava, 2023).

Safety

Data from Study 311 Part 1 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). The monovalent vaccine (Omicron BA.1), the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) demonstrated an acceptable safety profile when administered as a single dose in COVID-19 vaccine-experienced adult participants. The local and systemic reactogenicity profile reported in this study was consistent with the safety profile of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) reported in previous studies (see Decision Memorandum) (Dunkle, et al., 2022; Mallory, et al., 2022). No imbalances were identified in the percentages of serious and nonserious unsolicited adverse events, and no deaths occurred. No new safety concerns were identified.

6.4 Study 311, Part 2

Part 2 of Study 2019nCoV-311 (Study 311 Part 2) was a Phase 3 study evaluating the immunogenicity and safety of an updated monovalent vaccine (Omicron BA.5) administered as a single dose following previous vaccination with another authorized or approved COVID-19 vaccine (i.e., heterologous "booster" dose). The study was initiated on March 22, 2023 (first participant screened) and completed enrollment on May 2, 2023. An ad-hoc Day 189 interim analysis was performed at the request of FDA to provide 6-month safety data from the first dose of study vaccine with a data cutoff date of November 22, 2023, and a data extraction date of February 7, 2024. The final safety analysis includes data collected through a median of 220 days (7 months) in 764 participants.

6.4.1 Objectives

Primary Objective

The primary objective of Study 311 Part 2 was to determine if a single "booster" dose of the bivalent vaccine (Original and Omicron BA.5) induces superior neutralizing antibody responses compared with those following a single "booster" dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in participants previously vaccinated with at least 3 doses of an mRNA COVID-19 vaccine (any combination of Pfizer-BioNTech and/or Moderna original monovalent and/or bivalent COVID-19 vaccines).

Secondary Objectives

- To assess the neutralizing antibody immune responses induced by the bivalent vaccine (Original and Omicron BA.5), monovalent vaccine (Omicron BA.5), and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain.
- To assess the overall safety of 1-dose regimens containing the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), or bivalent vaccine (Original and Omicron BA.5)

Exploratory Objective

- To assess neutralizing antibody responses to the monovalent vaccine (Omicron BA.5).

6.4.2 Design Overview

Study 311 Part 2 was a Phase 3, randomized, observer-blinded study designed to compare the immune responses following a single "booster" dose of the bivalent (Original and Omicron BA.5) vaccine with those following a single "booster" dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adults 18 years of age and older. This study also included exploratory endpoints to evaluate immune responses to the monovalent vaccine (Omicron BA.5). These exploratory endpoints are a primary focus of the FDA immunogenicity analyses due to their relevance to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) under consideration in this BLA. (For additional details on study endpoints, see Section 6.4.8).

All enrolled participants had received at least 3 previous doses of an mRNA COVID-19 vaccine, with the last dose administered ≥90 days prior to randomization. A total of 766 medically stable adult participants were randomized 1:1:1 to one of 3 groups on Day 0:

Group F: Single dose monovalent valent (Omicron BA.5) (n=255)
Group G: Single dose Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (n=252)

Group H: Single dose bivalent valent (Original and Omicron BA.5) (n=259)

Randomization was stratified by age (18 through 54 years of age and ≥55 years of age). Although Study 311 Part 2 administered a second dose of vaccine to participants on Day 90, only immunogenicity data from the single dose administered on Day 0 were included in the interim study analysis and are included in the immunogenicity analysis section of this review (see Section 6.4.11). Safety data from both doses (Day 0 and Day 90) are included in the safety analyses section of this review (see Section 6.4.12).

6.4.3 Population

The study enrolled nonpregnant, non-lactating individuals 18 years of age and older at screening who were willing and able to give informed consent prior to study enrollment and to comply with study procedures, were medically stable, who agreed not to participate in any other SARS-CoV-2 prevention or treatment trials for the duration of the study, and who had previously received 3 doses of the Moderna and/or Pfizer-BioNTech COVID-19 prototype vaccines.

Key exclusion criteria were the same as in Study 311 Part 1 (see Section.6.3).

6.4.4 Study Treatments or Agents Mandated by the Protocol

The 3 study treatments were Matrix-M-adjuvanted, SARS-Co-V-2 recombinant spike (rS) protein-based COVID-19 vaccines, each containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered as an intramuscular injection:

- NVX-CoV2540 monovalent vaccine (Omicron BA.5)
  - Dose 0.5mL (5 µg/ 50 µg), lot # 5162Z001
- Original Monovalent Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
  - Dose 0.5mL (5 µg/ 50 µg), lot # 4302MF003
- Original Monovalent + NVX-CoV2540 bivalent vaccine (Original and Omicron BA.5)
  - Dose 0.5mL [5 µg/ 50 µg (total)]

6.4.5 Directions for Use

One intramuscular injection of monovalent vaccine (Omicron BA.5) or Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or bivalent vaccine (Original and Omicron BA.5) was administered on Day 0. Detailed instructions for vaccine preparation and administration were described in the Fact Sheet for Healthcare Providers for Novavax COVID-19 Vaccine, Adjuvanted.

6.4.6 Sites and Centers

Participants were enrolled at 20 clinical sites in Australia.

6.4.7 Surveillance/Monitoring

Immunogenicity (Laboratory Assays)

Blood samples for immunogenicity assessments were collected before vaccination on Day 0 and on Days 14 and 28. Samples were analyzed using validated pseudovirus neutralization assays with an inhibitory dilution of 50% (ID_{50}) to determine Omicron BA.5 sublineage-specific, ancestral (Wuhan) strain-specific, and XBB.1.5 sublineage-specific neutralizing antibody titers.

Safety Monitoring

Participants remained under observation for at least 30 minutes postvaccination to be monitored for any immediate hypersensitivity reactions (e.g., anaphylaxis). Participants used an eDiary to record reactogenicity (solicited AEs) on the day of vaccination and for an additional 6 days postvaccination. Unsolicited AEs were collected through Day 28 postvaccination. Collection of treatment-related medically attended adverse events (MAAEs), adverse event of special interest (AESIs), and serious adverse events (SAEs) were planned through 8 months postvaccination.

AESIs included myocarditis/pericarditis, potential immune-mediated medical condition (PIMMCs), and complications of COVID-19. Confirmed symptomatic cases of COVID-19 were recorded as adverse events, SAEs, or AESIs as appropriate.

6.4.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints

Immune responses at 28 days postvaccination were assessed descriptively based on neutralizing antibody GMTs and seroresponse rates (SRRs) to the BA.5 sublineage (exploratory) and to the ancestral (Wuhan) strain (secondary) to evaluate the following:

- Superiority of the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for neutralizing antibody geometric mean titers (GMTs) generated against the Omicron BA.5 sublineage.
- Noninferiority of the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for neutralizing antibody GMTs against the ancestral (Wuhan) strain.
- Noninferiority of the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) by percentage difference of SRRs for neutralizing antibodies against the ancestral (Wuhan) strain.

The following prespecified success criteria were applied to the 3 co-primary endpoints for the bivalent vaccine (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent):

- Superiority of neutralizing antibody GMTs generated against the Omicron BA.5 sublineage, which required a lower bound of 2-sided 95% confidence interval (CI) for the geometric mean titer ratio (GMTR) of the bivalent vaccine (Original and Omicron BA.5) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) greater than 1.0.
- Noninferiority by the percentage difference of SRRs for neutralizing antibodies to the Omicron BA.5 sublineage, which required a lower bound of the two-sided 95% CI of the estimated percentage difference in SRRs (bivalent vaccine [Original and Omicron BA.5] minus Novavax COVID-19 Vaccine, Adjuvanted [Original monovalent]) greater than -5%.
- Noninferiority for neutralizing antibody GMTs against the ancestral (Wuhan) strain, which required a lower bound of 2-sided 95% CI for GMTR of the bivalent vaccine (Original and Omicron BA.5) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) greater than 0.67, representing a 1.5-fold difference.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Please see Section 6.4.8 for immunogenicity statistical analysis plan.

AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using System Organ Class (SOC) and Preferred Term (PT) according to MedDRA.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

- Randomized population: all participants who were enrolled and randomized, regardless of whether they received any study vaccine.
- Immunogenicity population: all randomized participants who received the study vaccine according to protocol, had no major protocol deviations or an event (e.g., COVID-19 infection) that was considered clinically relevant to impact immunogenicity response, and who completed the study blood tests.
- The Per-Protocol (PP) Analysis Set included all participants who had a negative polymerase chain reaction (PCR) test for prior SARS-CoV-2 infection at baseline prior to vaccination, received the study vaccine according to protocol, and completed the study blood tests (a total of 693 participants on Day 28).
- Safety population: all randomized participants who received 1 dose of study vaccine through the data extraction date of April 5, 2024. Of the 831 randomized participants, 829 received a study vaccine, all of whom were included in the Safety Analysis Set.

6.4.10.1.1 Demographics

In the safety population of 764 participants, the median age was 43 years (range of 18-83 years across the 3 groups), and 632 (82.7%) participants were 18 through 54 years of age while 132 participants (17.3%) were 55 years of age and older. More than half of the participants in each group were female (53.7% to 55.8%) and the majority were White (76.8% to 83.0%) and Australian (86.5% to 88.0%). Most participants reported no history of COVID-19 infection (93.1% to 94.9%); however, the majority of participants were anti-N/polymerase chain reaction (PCR) positive at screening (73.3% to 79.5%). The median time between the most recent mRNA COVID-19 vaccine and the administered dose of study vaccine was approximately 12 months (328, 389, and 361 days in each of the vaccine groups, respectively). Overall, demographics and baseline disease characteristics were balanced across the 3 study vaccine groups.

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All participants enrolled in the study were medically stable with no autoimmune or immunodeficiency conditions requiring ongoing immunomodulatory therapy.

6.4.10.1.3 Participant Disposition

Of the 837 screened individuals, 766 were randomized to receive vaccination, 729 (95.2%) completed the study, and 37 (4.8%) discontinued study participation as of the data cutoff date of November 20, 2023. These discontinuations included 14 (5.5%) participants in the monovalent vaccine (Omicron BA.5) group, 14 (5.6%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 9 (3.5%) participants in the bivalent vaccine (Original and Omicron BA.5) group. The most common reason for discontinuation was lost to follow-up followed by participant decision to withdraw from the study. Two (0.3%) participants withdrew from the study due to an adverse event, 1 from the monovalent vaccine (Omicron

BA.5) group and 1 from the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group (See Section 6.4.12.7 for adverse events leading to study discontinuations)

The full analysis set was comprised of 764 randomized participants who received at least 1 dose of study vaccine, regardless of protocol violations or missing data, including 251 who received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), 254 who received monovalent vaccine (Omicron BA.5), and 259 who received bivalent vaccine (Original and Omicron BA.5).

Clinical Reviewer Comment: Discontinuations were balanced across all 3 vaccine groups, and study discontinuations due to adverse events occurred in only 2 participants.

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

The table below presents the geometric mean serum neutralizing antibody titers (ID_{50}) generated by the bivalent vaccine (Original and Omicron BA.5) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron BA.5 pseudovirus.

Table 94. Serum Neutralizing Antibody Titers Against the Omicron BA.5 Pseudovirus Following Initial Study Vaccination, Per-Protocol Neutralization Assay Subset, Part 2 Study 311

Parameter	Group F Monovalent (Omicron BA.5) N=238	Group G Original Monovalent N=228	Group H Bivalent (Original and Omicron BA.5) N=235
Baseline pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	238	228	235
Median	392.0	401.0	360.0
Minimum-maximum	18-27025	18-33971	18-35387
GMT	**353.9**	**332.0**	**300.2**
95% CI	288.0, 435.0	264.8, 416.1	243.4, 370.2
Day 28 pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	238	228	235
Median	1602.5	677.5	1267.0
Minimum-maximum	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[a]	1289.9	517.6	1042.0
95% CI	1130.1, 1472.4	452.5, 592.1	912.8, 1189.5

Parameter	Group F Monovalent (Omicron BA.5) N=238	Group G Original Monovalent N=228	Group H Bivalent (Original and Omicron BA.5) N=235
GMFR between visit and baseline	--	--	--
n2	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	--	--	--
n3	108	28	95
Percentage	45.4	12.3	40.4
95% CI	38.9, 51.9	8.3, 17.3	34.1, 47.0

Source: Table 14.2.1.1.1s in the eSub 3 CSR Addendum to Study 311 Part 2 "
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inhibitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate
N=number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set.
n1=Number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set within each visit with non-missing data.
n2=Number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set with non-missing data at both Day 0 and Day 28.
n3=Number of participants achieving seroresponse.
a. An analysis of covariance (ANCOVA) with vaccine group and age group (18-54 years, ≥55 years) as fixed effects and baseline value (Day 0) as covariate is performed to estimate the adjusted GMT and GMTR. The mean difference between vaccine groups and the corresponding CI limits is then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs.

The table below shows the geometric mean serum neutralizing antibody titer (ID_{50}) ratios on Day 28 postvaccination against the Omicron BA.5 pseudovirus.

Table 95. Comparison of Serum Neutralizing Antibody Titer Ratios Against the Omicron BA.5 Pseudovirus Following Initial Study Vaccination, Per-Protocol Neutralization Assay Subset, Part 2 Study 311

Comparison Between Groups	Monovalent (Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Monovalent (Omicron BA.5)
GMTR[a]	2.5	2.0	0.8
95% CI	2.11, 2.94	1.72, 2.37	0.68, 0.95
Difference in SRRs[b], %	33.1	28.1	-5.0
95% CI	25.3, 40.6	20.5, 35.6	-13.8, 4.0

Source: Adapted from Table 14.2.1.1.1s in the eSub 3 CSR Addendum to Study 311 Part 2
Abbreviations: CI=confidence interval; GMTR=ratio of GMT between groups; SRR=seroresponse rate
a. An analysis of covariance (ANCOVA) with vaccine group and age group (18-54 years, ≥55 years) as fixed effects and baseline value (Day 0) as covariate is performed to estimate the adjusted GMT and GMTR. The mean difference between vaccine groups and the corresponding CI limits is then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs.
b. 95% CI for the percentage difference in SRRs is calculated based on the method of Miettinen and Nurminen.

The immunogenicity analyses summarized below comparing the bivalent vaccine (Original and Omicron BA.5) with Original monovalent vaccine support inferring effectiveness of the updated bivalent formulation, which also met noninferiority criteria for the Original Wuhan strain.

Immunogenicity against the Omicron BA.5 sublineage:

- GMTR (Original and Omicron BA.5)/Original): 2.0 (95% CI: 1.72, 2.37)
    - Superiority criterion of a lower limit of the 95% CI >1 met
- SRR bivalent vaccine (Original and Omicron BA.5) minus Original monovalent vaccine

with respect to the Omicron BA.5 sublineage: 28.1% (95% CI: 20.5, 35.6);

- Noninferiority criterion of a lower limit of the 95% CI >-5% met

Clinical Reviewer Comment: While the above immunogenicity analyses for the bivalent vaccine (Original and Omicron BA.5) meet superiority success criteria when compared with the Original monovalent vaccine, no hypothesis testing was conducted to evaluate the noninferiority of the bivalent vaccine (Original and Omicron BA.5) compared with the monovalent vaccine (Omicron BA.5). As shown in Table 95, when this noninferiority analysis is conducted descriptively, the bivalent vaccine (Original and Omicron BA.5) lower limit of the 95% CI of the GMTR marginally exceeded 0.67, the standard criteria for showing noninferiority compared with the monovalent vaccine (Omicron BA.5) [GMTR 0.8 (95% CI: 0.68, 0.95)], but the percentage difference in SRR LB of 95% CI did not exceed -10.0%, the standard criteria for showing noninferiority with the monovalent vaccine [difference in SRR -5.0% (95% CI: -13.8, 4.0)]. As a bivalent vaccine was not being considered for authorization, immunogenicity of the monovalent vaccine (Omicron BA.5) was the basis for supporting regulatory decisions regarding the authorization of an updated monovalent vaccine formula. Please see the below analyses of secondary and exploratory endpoints for the aspects of our review most relevant to evaluating the effectiveness of monovalent vaccine (Omicron BA.5).

6.4.11.2 Analyses of Secondary Endpoints

Secondary endpoints evaluating neutralizing antibody immune responses induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against the ancestral (Wuhan) pseudovirus were analyzed descriptively. The PP Analysis Set immunogenicity results for the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) on Day 28 postvaccination against the ancestral (Wuhan) pseudovirus were as follows:

Monovalent Vaccine (Omicron BA.5) Descriptive Analysis on Day 28

- Estimated GMTR (Omicron BA.5)/(Original monovalent) against the ancestral (Wuhan) pseudovirus: 0.9 (95% CI: 0.78, 1.08) (the lower limit of the 95% CI around the GMTR is >0.67).
- Estimated percentage difference in SRRs (Omicron BA.5) minus (Original monovalent) against the ancestral (Wuhan) pseudovirus: -0.4% (95% CI: -8.1, 7.2) (the lower limit of the 95% CI around the percentage difference in SRRs is >-10%).

Clinical Reviewer Comment: The above immunogenicity results, analyzed descriptively, met the expected lower limits of the 95% CIs for both GMTR and the percentage difference in SRRs necessary to demonstrate comparable immune responses between the monovalent vaccine (Omicron BA.5) and Original monovalent vaccine. These data are supportive of the effectiveness of a single dose of monovalent vaccine (Omicron BA.5) against the ancestral (Wuhan) pseudovirus, which provides a descriptive immune bridge between the monovalent vaccine (Omicron BA.5) immune responses and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) efficacy against the ancestral (Wuhan) pseudovirus in Study 301.

6.4.11.3 Subpopulation Analyses

Descriptive analyses of the primary endpoints were performed separately by age group (18 through 54 years versus 55 years and older) and SARS-CoV-2 anti-N positivity at baseline.

Descriptive Subgroup Analysis by Age

A single dose of monovalent vaccine (Omicron BA.5) induced the following neutralizing antibody responses against the Omicron BA.5 subvariant pseudovirus on Day 28 in the PP Analysis Set:

- 18 through 54 years of age (n=199)
    - The GMT increased 4.3-fold from baseline of 400.9 (95% CI: 322.8, 497.9) to a Day 28 GMT of 1706.5 (95% CI: 1411.5, 2063.2).
    - The estimated GMTR of the monovalent vaccine (Omicron BA.5) versus Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against Omicron BA.5 sublineage was 2.5 (95% CI: 2.10, 3.01).
    - The estimated percentage difference in SRRs of the monovalent vaccine (Omicron BA.5) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.5 sublineage was 32.1% (95% CI: 23.5, 40.3).
- ≥55 years of age (n=39)
    - The GMT increased 4.6-fold from baseline of 187.4 (95% CI: 104.3, 336.6) to a Day 28 GMT of 869.2 (95% CI: 523.5, 1443.1).
    - The estimated GMTR of the monovalent vaccine (Omicron BA.5) versus Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against Omicron BA.5 sublineage was 2.5 (95% CI: 1.61, 3.87).
    - The estimated percentage difference in SRRs of the monovalent vaccine (Omicron BA.5) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.5 sublineage was 38.3% (95% CI: 19.5, 55.2).

Descriptive Subgroup Analysis by Anti-Nucleocapsid Serostatus

By Day 28 postvaccination, neutralizing antibody titers in a subgroup of anti-N negative participants (n=54) rose 6-fold from baseline GMT 79.16 (95% CI: 50.73, 123.51) to GMT 472.82 (95% CI: 292.05, 765.48) compared with a subgroup of anti-N positive participants (n=185) with a nearly 4-fold rise from baseline GMT 549.75 (95% CI: 453.93, 665.81) to 2155.73 (95% CI: 1843.64, 2520.66).

> *Clinical Reviewer Comment: While these descriptive immunogenicity data for monovalent vaccine (Omicron BA.5) subgroup analysis by age cannot be interpreted due to the small sample size, the descriptive efficacy analysis conducted in geriatric participants ≥65 years of age compared with younger participants receiving the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in Study 301 suggest that vaccine efficacy may be lower for individuals ≥65 years of age than in individuals 18 through 64 years of age but still supportive of meaningful clinical benefit in the geriatric population (see Section 6.1.11). Additionally, descriptive age subgroup analysis based on immunogenicity data in Study 313 provide support for the effectiveness of a single dose of updated monovalent vaccine in participants ≥55 years of age (see Section 6.5.11.3).*

Descriptive Subgroup Analysis by Anti-Nucleocapsid Serostatus

By Day 28 postvaccination, neutralizing antibody titers in a subgroup of anti-N negative participants (n=54) rose 6-fold from baseline GMT 79.16 (95% CI: 50.73, 123.51) to GMT 472.82 (95% CI: 292.05, 765.48) compared with a subgroup of anti-N positive participants (n=185) with a nearly 4-fold rise from baseline GMT 549.75 (95% CI: 453.93, 665.81) to 2155.73 (95% CI: 1843.64, 2520.66).

Clinical Reviewer Comment: Subgroup analysis by anti-N serostatus at baseline is inconclusive, as there is no antibody titer level known to be a correlate of protection against COVID-19, and it is not possible to draw definitive conclusions about the postvaccination neutralizing antibody titer levels in those with and without evidence of prior natural SARS-CoV-2 infection.

6.4.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.4.10 for a summary of participant discontinuation.

6.4.11.5 Exploratory and Post Hoc Analyses

The following neutralizing antibody responses were generated by the monovalent vaccine (Omicron BA.5) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron BA.5 pseudovirus on Day 28 postvaccination:

Monovalent Vaccine (Omicron BA.5) Descriptive Analysis:

- The estimated GMTR of the monovalent vaccine (Omicron BA.5) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.5 sublineage was 2.5 (95% CI: 2.10, 2.94) (the lower limit of the 95% CI around the GMTR is >1).
- The estimated percentage difference in SRRs of the monovalent vaccine (Omicron BA.5) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.5 sublineage was 33.2% (95% CI: 25.4, 40.7) (the lower limit of the 95% CI around the percentage difference in SRRs is >-5%).

Clinical Reviewer Comment: The above descriptive analyses of the exploratory endpoints to evaluate immune responses to the monovalent vaccine (Omicron BA.5) against the Omicron BA.5 sublineage were the focus of the FDA analysis due to their relevance for the monovalent vaccine formulation and indication under review. This exploratory endpoint analysis shows that the monovalent vaccine (Omicron BA.5) induces superior neutralizing antibody responses (as measured by GMTR) and noninferior responses (as measured by the percentage difference in SRRs) when compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Taken together with the noninferiority analysis of secondary endpoints for the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain (see Section 6.4.11.2), the secondary and exploratory endpoint analyses provide an immune bridge between the monovalent vaccine (Omicron BA.5) immune responses and those induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to support the effectiveness of the updated monovalent vaccine (Omicron BA.5). Based on the inferred effectiveness of this monovalent vaccine (Omicron BA.5), it is reasonable to expect that updated subvariant monovalent Novavax COVID-19 vaccines manufactured using similar technology will have comparable effectiveness.

Although an assessment of antibody responses against the Omicron XBB 1.5 subvariant were not pre-specified in the protocol, this analysis was conducted post-hoc to assess vaccine activity against a circulating subvariant. The monovalent vaccine (Omicron BA.5) induced the following neutralizing antibody responses against the Omicron XBB.1.5 pseudovirus displayed in the following table.

Table 96. Serum Neutralizing Antibody Titers Against the Omicron XBB.1.5 Pseudovirus Following Initial Vaccination, Per-Protocol Immunology Subset, Part 2 Study 311

Parameter	Group F Monovalent (Omicron BA.5) N=236	Group G Original Monovalent N=227	Group H Bivalent (Original and Omicron BA.5) N=231
Baseline pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	236	227	231
Median	73.0	69.0	67.0
Minimum-maximum	19-7822	19-58552	19-30277
GMT	**95.6**	**100.0**	**93.0**
95% CI	79.4, 115.2	80.8, 123.8	76.8, 112.6
Day 28 pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	236	227	231
Median	366.0	136.0	271.0
Minimum-maximum	19-17254	19-14790	19-15557
GMT	**374.9**	**145.8**	**261.5**
95% CI	**313.5, 448.3**	**119.4, 177.9**	**217.7, 314.2**
Adjusted GMT[a]	332.9	125.9	238.3
95% CI	290.5, 381.6	109.7, 144.5	208.0, 273.1
GMFR between visit and baseline	--	--	--
n2	236	227	231
Reference to Day 0	3.9	1.5	2.8
95% CI	3.4, 4.6	1.3, 1.6	2.5, 3.2
Seroresponse from baseline	--	--	--
n3	93	16	59
Percentage	**39.4**	**7.0**	**25.5**
95% CI	**33.1, 46.0**	**4.1, 11.2**	**20.0, 31.7**

Source: Table 14.2.1.3.1 in the "14.2 Efficacy Data Summary Figures and Tables"
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inhibitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
N=number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set.
n1=Number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set within each visit with non-missing data.
n2=Number of participants in the assay-specific Per-Protocol Immunogenicity Analysis Set with non-missing data at both Day 0 and Day 28.
n3=Number of participants achieving seroresponse.
a. An analysis of covariance (ANCOVA) with vaccine group and age group (18-54 years of age, ≥55 years of age) as fixed effects and baseline value (Day 0) as covariate is performed to estimate the adjusted GMT and GMTR. The mean difference between vaccine groups and the corresponding CI limits is then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs.

Table 97. Comparison of Serum Neutralizing Antibody Titer Ratios Against the Omicron XBB.1.5 Pseudovirus on Day 28 Following Initial Vaccination, Per-Protocol Immunology Subset, Part 2 Study 311

Comparison Between Groups	Monovalent (Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Monovalent (Omicron BA.5)
GMTR[a]	2.65	1.96	0.74
95% CI	(2.23, 3.15)	(1.66, 2.3)	(0.61, 0.88)
Difference in SRRs[b], %	32.06	19.03	-12.69
95% CI	(24.98, 39.07)	(12.58, 25.65)	(-20.98, -4.24)

Source: Reviewer Table, compiled from datasets submitted to BLA 125817/0.15
Abbreviations: CI=confidence interval; GMT=geometric mean titer; ID_{50}=50% inhibitory dilution; GMTR=ratio of GMT between groups; SRR=seroresponse rate.
a. An analysis of covariance (ANCOVA) with vaccine group and age group (18-54 years, ≥55 years) as fixed effects and baseline value (Day 0) as covariate is performed to estimate the adjusted GMT and GMTR. The mean difference between vaccine groups and the corresponding CI limits is then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs.
b. 95% CI for the percentage difference in SRRs is calculated based on the method of Miettinen and Nurminen

As shown in the descriptive post hoc analysis in the previous table, the monovalent vaccine (Omicron BA.5) induced immune responses that exceeded the standard criteria for showing superiority in terms of the GMTR [2.6 (95% CI: 2.23,3.15)] and for showing noninferiority in terms of the difference in SRRs [percentage difference in SRRs of 32.4% (95% CI: 25.2, 39.4)] against the Omicron XBB.1.5 sublineage as compared with those of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) on Day 28 postvaccination (based on the standard criteria of superiority [LB of 95% CI >1] and noninferiority [LB of 95% CI >-5%]).

However, the bivalent vaccine (Original and Omicron BA.5) lower limit of the 95% CI of the GMTR did not exceed 0.67, the standard criteria for showing noninferiority compared with the monovalent vaccine (Omicron BA.5) [GMTR 0.74 (95% CI: 0.61, 0.88)]. In addition, the lower limit of the 95% CI of the percentage difference in SRRs did not exceed -10.0% that would have been necessary to show noninferiority by the percentage difference in SRRs [-12.69% (95% CI: -20.98%, -4.24%)]. These were post hoc descriptive analyses and were not performed while adjusting for multiplicity.

> *Reviewer Comment: The monovalent vaccine (Omicron BA.5) induced neutralizing antibodies that demonstrated a level of vaccine cross-reactivity against a circulating Omicron XBB-lineage virus. These results add support for the effectiveness of the monovalent vaccine technology against circulating variants of concern beyond the Omicron BA.5 lineage.*

6.4.12 Safety Analyses

6.4.12.1 Methods

Please see Section 6.4.7.

6.4.12.2 Overview of Adverse Events

Study 311 Part 2 safety data included solicited local AEs, solicited systemic AEs, unsolicited AEs, treatment-related unsolicited AEs, and a median of 220 days of safety follow-up for MAAEs (treatment-related), SAEs, and AESIs.

The table below presents an overall summary of solicited and unsolicited AEs.

Table 98. Frequency and Percentage of Solicited and Unsolicited Adverse Events Following Initial Booster Vaccination With Monovalent (Omicron BA.5), Original Monovalent, or Bivalent (Original and Omicron BA.5) Until End of Study in Adult Participants Who Previously Received ≥3 Vaccinations with COVID-19 mRNA Vaccines, Safety Analysis Set, Part 2 Study 311

Adverse Event	Group F Monovalent (Omicron BA.5) N=254 n (%)	Group G Original Monovalent N=251 n (%)	Group H Bivalent (Original and Omicron BA.5) N=259 n (%)
Solicited AEs within 7 days (Days 0 to 6) after vaccination	--	--	--
Any solicited AE[b]	187 (74.2)	196 (78.1)	204 (78.8)
Grade 3 or higher	7 (2.8)	12 (4.8)	10 (3.9)
Any Solicited AE of Grade 4	0	0	0
Unsolicited AEs through 28 days after vaccination	--	--	--
Any TEAEs	81 (31.9)	87 (36.7)	82 (31.7)
Related TEAEs	6 (2.4)	6 (2.4)	10 (4.2)
Severe TEAEs	2 (0.8)	2 (0.8)	3 (1.2)
Related Severe TEAEs	0	0	1 (0.4)
Any MAAEs	35 (13.8)	43 (17.1)	34 (13.1)
Severe MAAEs	1 (0.4)	2 (0.8)	1 (0.4)
Unsolicited AEs from first booster until EoS	--	--	--
Related Severe MAAEs	0	0	0
Related MAAEs	1 (0.4)	1 (0.4)	3 (1.2)
Related Serious MAAEs	0	0	0
Any Serious TEAEs	7 (2.8)	10 (4.8)	3 (1.2)
Related Serious TEAEs	1 (0.4)	0	1 (0.4)
Any AESIs (PIMMCs)[a]	2 (0.8)	1 (0.4)	2 (0.8)
Related AESIs (PIMMCs) [1]	1 (0.4)	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	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
Related TEAEs Leading to Study Discontinuation	0	0	0

Source: Adapted from Study 311 Part 2. Table 80, T14.3.1.2, and Table 14.3.2.1 submitted to EUA 28237/130.
Abbreviations: AE=adverse event; AESIs=adverse event(s) of special interest; CRF=case report form; EoS=end of study; MAAE=treatment-emergent medically attended adverse event; N=Number of participants in the Safety Analysis Set who received the first dose within each treatment; n=number of participants at each level of summarization; PIMMC=potential immune-mediated medical conditions; TEAE=treatment emergent adverse event.
a. PIMMCs according to Protocol-defined Criteria or Investigator Reported in CRF.
b. Solicited adverse reaction percentages are reported based on the 252, 251, and 259 participants who completed eDiary solicited ARs in Group F, G, and H, respectively.
Note: If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), then it was recorded as an AE with the start date the 7th day after the relevant study vaccination and followed to resolution. Solicited AEs that continue past Day 6 were not

included in this summary. At each level of participant summarization, a participant was counted once if the participant reported one or more events.
Note: Relationship and severity were based on the data reported by Site – i.e., missing information was not imputed. Note: MAAE, serious TEAE, PIMMC, AESI (COVID-19), and TEAEs leading to any discontinuation are reported through the second booster vaccination or data cutoff date whichever was earlier. Other TEAEs with start date within 28 days post first vaccination are reported.

Solicited Adverse Reactions

The percentages of participants reporting local injection site ARs were relatively balanced across the 3 vaccine groups, occurring with percentages of 60.7%, 66.9%, and 65.3% in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively. Injection site pain and/ or tenderness were the most common injection site ARs reported. Redness and swelling were reported in less than 4% of participants in any group. Grade 3 local solicited ARs were rare (less than 2% of all participants for any event in each group) and no Grade 4 ARs were reported.

Across the vaccine groups, the median duration of solicited local injection site ARs was 2.0 days for pain/tenderness, between 1.5 to 2.0 days for redness, and between 1.5 to 2.5 days for swelling. One solicited local injection site AR persisted beyond 7 days (pain/tenderness lasting 9 days).

The percentages of participants reporting solicited systemic ARs were balanced across the 3 vaccine groups: 56.3%, 55.4%, and 59.8% for the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.5) groups, respectively. Fatigue/ malaise, headache, and muscle pain were the most frequent solicited systemic ARs (reported by >20% of participants across all 3 vaccine groups). No solicited systemic grade 4 ARs were reported in any vaccine group.

Solicited ARs were reported at higher percentages in younger participants 18 to 54 years of age (78.0% to 81.1%) than in older participants 55 years of age and older (55.8% to 68.1%). Slightly higher percentages of solicited ARs were also reported by females (88.6% to 92.9%) than males (72.6% to 80.8%) across all vaccine groups.

The race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Unsolicited AEs

Unsolicited AEs were reported by similar rates of individuals across the 3 vaccine groups. The most frequently reported were in the MedDRA SOC of *Infections and Infestations* (reported by 7.9% to 12.0% of participants across the 3 vaccine groups), with upper respiratory tract infection being the most commonly reported MedDRA PT, occurring in 8 (3.1%), 11 (4.4%) and 14 (5.4%) of participants in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively.

Severe unsolicited AEs were reported by 1 participant (0.4%) in the Original monovalent group who experienced a generalized reaction to an influenza vaccine and by 3 (1.2%) participants in the bivalent vaccine (Original and Omicron BA.5) group who experienced limb injury, pelvic pain, and diarrhea, respectively.

Treatment-related unsolicited AEs were reported by 1.2%, 2.0%, and 3.1% of participants in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively. The most

frequently reported event was lymphadenopathy: 0, 0.8%, and 1.2% in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively. All were mild in severity except for a moderate event of migraine headache in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, a moderate event of VIth cranial nerve palsy in the bivalent vaccine (Original and Omicron BA.5) group, and the severe event of diarrhea in the bivalent vaccine (Original and Omicron BA.5) group.

MAAEs

MAAEs through 28 days were reported by 9.1%, 11.6% and 8.1% of participants in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively. MAAEs were most frequently reported in the MedDRA SOC of *Infections and Infestations* (reported by fewer than 4% of participants across the 3 vaccine groups). Within this SOC, Upper respiratory infection was the most commonly reported PT, reported by 1.2%, 0.8%, and 0.4% of participants in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively.

Treatment-related MAAEs were collected through the end of study and were reported by 5 participants: 1 (0.4%) in the monovalent vaccine (Omicron BA.5) group with rash, 1 (0.4%) in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with pruritus, and 3 (1.2%) in the bivalent vaccine (Original and Omicron BA.5) group [1 with upper respiratory tract infection, 1 with musculoskeletal chest pain, and 1 with deep vein thrombosis (DVT)].

Based on subgroup analyses, no notable differences were observed for MAAEs by age, sex, race, or ethnicity, although many of these analyses were limited due to the low number of participants with MAAEs in many subgroups.

> *Clinical Reviewer Comment: The treatment-related DVT occurred 10 days after the 2nd dose of bivalent vaccine in a 56-year-old male with obesity (BMI of 35) on no concomitant medication. The event was considered nonserious, moderate in severity, did not lead to study discontinuation, and was treated with anticoagulation. This reviewer agrees with the Investigator's assessment of possible relatedness to the study vaccine. Though this single case of DVT in Study 311 is insufficient to establish a safety signal, in the context of the Study 301 data, thrombotic events are included in Section 6.1 of the USPI. For further discussion, please see Adult Main Study 301 Embolic and Thrombotic Events in Section 6.1.12.5. on Adverse Events of Special Interest (AESI).*

6.4.12.3 Deaths

There were no deaths in the study.

6.4.12.4 Nonfatal Serious Adverse Events

A total of 26 SAEs were reported through the data cutoff date by 7 (2.8%), 10 (4.8%), and 3 (1.5%) of participants in the monovalent vaccine (Omicron BA.5) group, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and bivalent vaccine (Original and Omicron BA.5) group, respectively. In general SAEs were infrequent and generally similar between the treatment groups. Relevant narrative information for each participant who reported an SAE.

Of the 26 SAEs reported by 23 participants, the events of IVth and VIth cranial nerve paralysis are considered possibly related by FDA.

Cranial nerve paralysis

- An SAE of IVth cranial nerve palsy was reported by a 49-year-old White female in the monovalent vaccine (Omicron BA.5) group with a longstanding history of type 1 diabetes mellitus, hypertension, hypercholesterolemia, pneumonia, vitamin D deficiency, bilateral sensory neural hearing loss, and prior COVID-19 infection. The participant experienced a left-sided migraine 2 days postvaccination. Approximately 7 days postvaccination, she experienced both headache and double vision. A head computerized tomography (CT) was performed 9 days postvaccination that was negative for hemorrhage, space-occupying lesion, skull abnormality or any other cause of the symptoms reported. A subsequent head magnetic resonance imaging (MRI) was also negative. The participant was diagnosed by a neuro-ophthalmologist 37 days postvaccination with superior oblique IVth cranial nerve palsy. No medical treatment was given, by 56 days postvaccination, the symptoms were ongoing but slowly improving. A brain and orbit MRI with gadolinium performed 132 days postvaccination was notable for symmetrical superior oblique muscle bilaterally with normal enhancement and no evidence of superior oblique inflammation. By 145 days postvaccination, the participant's symptoms had resolved except for eye fatigue when tired, and the event was considered resolved. The Principal Investigator assessed the IVth cranial nerve palsy as moderate in intensity and related to the study vaccine. The Applicant assessed the event as not related to the study vaccine due to the participant's underlying type 1 diabetes and hypertension with associated microvascular disease that provides alternative causality.

Clinical Reviewer Comment: Although there are underlying predisposing conditions, due to the close temporal association to vaccination and biologic plausibility for a potential autoimmune mechanism, this reviewer considers this case of IVth cranial nerve paralysis to be possibly related to the study vaccine.

- An SAE of VIth cranial nerve palsy (originally classified by the Applicant as a non-serious AE but considered an SAE by FDA based on the criterion of important medical event) was reported by a 53-year-old White male in the bivalent vaccine (Original and Omicron BA.5) group with a history of arm neuropathy, type 1 diabetes, deep vein thrombosis, seizures, tobacco use, cerebrovascular accident, and diplopia in 2020 that self-resolved. The participant experienced the onset of blurriness/ double vision approximately 14 days postvaccination and was diagnosed with right eye VIth nerve palsy and residual right eye IVth nerve palsy, likely from a microvascular cause. The participant was discharged the same day with plans for brain/orbits MRI (unremarkable), CT brain, CT angiography, blood tests, and optimization of diabetes control. The results of these imaging studies were not provided. A neurologist attributed the diagnosis of VIth nerve palsy to a microvascular etiology associated with type 1 diabetes and possibly related to the patient's prior history of diplopia. A follow-up visit with Neurology was notable for resolution of symptoms. The event was considered resolved 84 days postvaccination. Initially, the Principal Investigator assessed this SAE to be moderate in severity and related to the study vaccine but later reassessed the SAE as not related to the study vaccine based on the neurologist's opinion that the cranial nerve palsy was secondary to type 1 diabetes mellitus. The Applicant considered the event not related to the study vaccine due to the type 1 diabetes and associated microvascular disease that provides alternative causality.

Clinical Reviewer Comment: Despite predisposing risk factors, this reviewer considers this case of cranial nerve VI paralysis to be possibly related to vaccination due to temporality and biological plausibility. These 2 cases of oculomotor cranial nerve paralysis were evaluated under Emergency Use Authorization of the 2023-2024 Formula, and in addition to the continued inclusion of these events in product labeling (see Section 6.1 of the USPI), this potential safety signal will be addressed via enhanced pharmacovigilance in postmarketing surveillance (see Section 11.6 for details).

Other SAEs

The remaining SAEs were not considered related to vaccine by the investigator and Applicant. Brief details of each SAE are provided below.

1. A 51-year-old White female, monovalent vaccine (Omicron BA.5) group, SAE of musculoskeletal (non-cardiac) chest pain 43 days after Dose 1 of study vaccine, resolved.

2. A 59-year-old White male, monovalent vaccine (Omicron BA.5) group, SAE of Achilles tendon rupture 43 days after Dose 1 of the study, resolved.

3. A 20-year-old Asian female, monovalent vaccine (Omicron BA.5) group experienced an SAE of peritonsillar abscess 121 days after Dose 1 and 24 days after receiving Dose 2 of study vaccine, resolved.

4. A 64-year-old White male, monovalent vaccine (Omicron BA.5) group, SAE of acute coronary syndrome 40 days after Dose 1 of study vaccine, resolved.

5. A 64-year-old White male, monovalent vaccine (Omicron BA.5) group, SAE of acute myocardial infarction approximately 32 days after Dose 1 of study vaccine, case complicated by concurrent COVID-19 infection, resolved.

6. A 46-year-old White female, monovalent vaccine (Omicron BA.5) group, SAE of acute cholecystitis 98 days after Dose 1 and 8 days after Dose 2 of study vaccination, resolved.

7. A 28-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of intentional overdose of multiple substances 137 days after Dose 1 and 46 days after Dose 2 of study vaccine, resolved.

   The same participant experienced a second SAE of suicidal ideation 142 days after dose 1 and 51 days after Dose 2 of study vaccine, resolved.

8. A 39-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of pain in the lower extremity 186 days after Dose 1 and 88 days after Dose 2 of study vaccine, resolved.

9. A 42-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of systemic infection related to a dog bite 70 days after Dose 1 of study vaccine, resolved.

10. A 42-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of a limb abscess of the right leg related to a bike injury 100 days after Dose 1 and 10 days after Dose 2 of study vaccine, resolved.

11. A 25-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of clavicle fracture 52 days after Dose 2 of study vaccine, resolved.

12. A 59-year-old White male, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of hypoglycemia 96 days after Dose 1 and 5 days after Dose 2 of study vaccine, resolved.

13. A 45-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of acute parotitis 247 days after Dose 1 and 156 days after Dose 2 of study vaccine, resolved.

14. A 29-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of pneumonia 112 days after Dose 1 and 21 days after Dose 2 of study vaccine, resolved.

15. A 51-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of COVID-19 pneumonia 202 days after Dose 1 and 103 days after Dose 2 of study vaccine, resolved.

16. A 49-year-old White male, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of gastric sarcoma 64 days after Dose 1 of study vaccine, resolved.

17. A 68-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, 2 SAEs of asthma and pneumonia 81 days after Dose 1 of study vaccine, resolved.

18. A 27-year-old White female, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAE of joint dislocation 224 days after Dose 1 and 131 days after Dose 2 of study vaccine, resolved.

19. A 60-year-old male, bivalent vaccine (Original and Omicron BA.5) group, SAE of cellulitis related to a tick bite 229 days after Dose 1 and 146 days after Dose 2 of study vaccine, resolved.

20. A 42-year-old White male, bivalent vaccine (Original and Omicron BA.5) group, SAE of limb injury 23 days after Dose 1, resolved.

21. A 56-year-old White female, bivalent vaccine (Original and Omicron BA.5) group, SAE of nephrolithiasis 231 days after Dose 1 and 139 days after Dose 2 of study vaccine, resolved.

There were no deaths reported in the study.

Reviewer Comment: This reviewer agrees with the assessment that each of these reported SAEs are not related to the study vaccine based on lack of temporal association, biological implausibility, and/or alternative etiology in each case.

6.4.12.5 Adverse Events of Special Interest (AESI)

Six participants experienced AESIs, 2 of which were considered related to the study vaccine by the Investigator:

One participant in the monovalent vaccine (Omicron BA.5) group experienced an SAE of acute myocardial infarction that was also categorized as an AESI complication due to COVID-19 (see narrative described above).

The 5 remaining AESI cases were categorized as potentially immune-mediated medical conditions (PIMMCs) based on protocol-defined criteria or investigator assessment.

1. The SAE of IVth cranial nerve paralysis in a 49-year-old White female in the monovalent vaccine (Omicron BA.5) group was also characterized as an AESI (PIMMC) and considered related to the study vaccine by the Investigator (see described above).

2. A 38-year-old White female in the monovalent vaccine (Omicron BA.5) group with a history of migraines, anxiety, bipolar affective disorder, excessive daytime somnolence, and concomitant medications of Topiramate, Lamotrigine, Agomelatine, and Diazepam experienced an AESI (PIMMC) of narcolepsy 98 days after Dose 1 and 7 days after Dose 2 of study vaccine. Five days after onset of sleep disturbances and excessive daytime sleepiness, a sleep specialist initiated modafinil treatment. Roughly 2 months after onset of symptoms, she underwent a diagnostic sleep study and was formally diagnosed with narcolepsy without cataplexy. The event was characterized as moderate in severity, was not resolved by the participant's last follow-up study visit and is considered an ongoing diagnosis. The Investigator and Applicant assessed the event as not related to the study vaccine, as the participant's underlying medical conditions and concomitant medications can provide an alternative explanation for sleep disturbances and daytime sleepiness.

3. A 41-year-old White female participant in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, with a history of migraine, night terrors, chronic pain, and depression, experienced an AESI (PIMMC) of vestibular neuronitis with onset of symptoms of nausea/ vomiting, vertigo, and headache 11 days after Dose 1 of study vaccine. She did not seek medical attention, and symptoms resolved spontaneously within 3 days. She experienced a second episode of vestibular neuronitis 16 days after the 2nd dose of study vaccine which resolved after 3 days with bedrest. The Investigator and Applicant assessed both events as related to the study vaccine.

4. The SAE of VIth nerve paralysis in a 53-year-old White male in the bivalent vaccine (Original and Omicron BA.5) group was characterized as an AESI (PIMMC) considered not related to the study vaccine by the Investigator and Applicant (see SAE narrative above). This same participant later experienced an AESI (PIMMC) of Bell's Palsy 99 days after the 2nd dose of study vaccine. Symptoms of left facial droop were abrupt in onset, he was evaluated in the emergency department, neuroimaging studies were performed, the diagnosis of Bell's palsy was made, and he was discharged. Outpatient treatment included valacyclovir and prednisone in tapering doses along with weekly intramuscular B-12 injections. By 4 months after onset of symptoms, the event was considered to be improving but not resolved. The Investigator assessed the event as moderate intensity and not related to the study vaccine, as microvascular disease associated with the participant's long history of type 1 diabetes can provide an alternative explanation.

5. A 48-year-old White female in the bivalent vaccine (Original and Omicron BA.5) group experienced an AESI (PIMMC) of Hashimoto's thyroiditis 23 days after Dose 1 of study vaccine. The diagnosis was made in the setting of a clinical workup for abnormal uterine bleeding. Treatment with oral thyroxine was initiated. By 8 months after onset of symptoms, the event was considered not resolved. The Investigator assessed the event as moderate in severity and not related to the study vaccine based on the participant's baseline laboratory tests showing elevated anti-thyroid peroxidase antibodies prior to study vaccination.

Clinical Reviewer Comment: This reviewer concurs with the Investigator that 3 out of the 7 AESI: PIMMC events (narcolepsy, Bell's palsy, and autoimmune thyroiditis) are unlikely to be related to the study vaccine and that 3 out of the 7 events (IVth cranial nerve paralysis and 2 episodes of vestibular neuronitis 11 and 16 days postvaccination) are likely related to the study vaccine based on the close temporal association and biologic plausibility of a potential autoimmune mechanism). However, this reviewer also considers the case of VIth cranial nerve paralysis to be potentially related to the study vaccine (see Clinical Reviewer Comment above).

Vestibular neuronitis, which involves inflammation of the VIIIth cranial nerve, has been described in the literature as a comorbidity associated with COVID-19 natural infection and COVID-19 vaccination along with other otorhinolaryngological disorders reported after COVID-19 vaccination including tinnitus and facial nerve paralysis (Kamogashira, et al., 2022). The occurrence of 3 treatment-related AESI: PIMMCs in this study involving cranial nerve disorders warrants inclusion in product labeling and enhanced postmarketing pharmacovigilance.

Subgroup analyses of SAEs by age, sex, race, and ethnicity were inconclusive as there were too few participants with serious events.

6.4.12.6 Clinical Test Results

All eligible female participants in Part 2 of the study had negative pregnancy tests at screening.

6.4.12.7 Dropouts and/or Discontinuations

See Section 6.4.10.1.3 for Participant Disposition summarizing early termination from the study.

AEs Leading to Vaccine or Study Discontinuation

Three participants reported AEs leading to vaccine discontinuation. One (0.4%) participant in the monovalent vaccine (Omicron BA.5) group experienced an unsolicited AE involving IVth cranial nerve paralysis (see SAE narrative above). Two (0.8%) participants in Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group experienced unsolicited AEs leading to study vaccination discontinuation: 1 participant with gastric sarcoma (see SAE narrative above) and 1 participant with asthma and pneumonia (see SAE narrative above).

One (0.4%) participant in the monovalent vaccine (Omicron BA.5) group experienced an unsolicited AE of tendon rupture leading to study discontinuation (see SAE narrative above). The participant in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group with gastric sarcoma who discontinued study vaccination also discontinued study participation.

6.4.13 Study Summary and Conclusions

Effectiveness

Study 311 Part 2 provides data, based on a descriptive analysis, demonstrating superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 18 years of age and older previously vaccinated with mRNA COVID-19 vaccines.

This study also provides supportive immunogenicity data, based on descriptive analysis, showing noninferior neutralizing antibody responses induced by the monovalent (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain. These analyses provide an immune bridge between the monovalent vaccine (Omicron BA.5) immune responses and those induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to support the effectiveness of the updated monovalent vaccine (Omicron BA.5).

However, neither the prespecified noninferiority analysis of the bivalent vaccine (Original and Omicron BA.1) compared with the monovalent vaccine (Omicron BA.1) vaccine (see Section 6.3.11.2) nor the descriptive noninferiority analysis of the bivalent vaccine (Original and Omicron BA.5) compared with the monovalent vaccine (Omicron BA.5) succeeded. Based on the available data, there is insufficient evidence to conclude that the bivalent vaccine technology would be effective for future formulations.

The bivalent mRNA vaccines were authorized based on noninferiority comparisons between the bivalent Omicron BA.4/5 “booster” vaccines and the Original monovalent vaccines. Novavax was able to provide similar evidence that their bivalent vaccine was superior to the Original monovalent vaccine. However, the data that failed to show noninferior immune responses between the monovalent vaccine (Omicron BA.1) and bivalent vaccine (Original and Omicron BA.1) confounded the ability to support labeling of a bivalent vaccine formulation based on the totality of evidence for the effectiveness of the bivalent vaccine technology.

Superior neutralizing antibody responses induced by the monovalent vaccine (Omicron BA.5) against Omicron BA.5 sublineage can also be extrapolated to adolescents 12 through 17 years of age in the context of previously reviewed comparable efficacy and immunogenicity results between adult and adolescents observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and comparable immunogenicity results between a 2-dose series and a 1-dose “booster” of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adolescents (see Decision Memorandum and Section 6.2).

Safety

The monovalent vaccine (Omicron BA.5), the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.5) had an acceptable safety profile when administered as a single dose in previously COVID-19 vaccinated participants 18 years of age and older. The local and systemic reactogenicity reported in this study was consistent with the known safety profile of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) seen in previous studies (see Decision Memorandum) (Dunkle, et al., 2022; Mallory, et al., 2022).

Three AESIs categorized as potentially immune-mediated medical conditions (1 case of vestibular neuronitis and 2 cases of oculomotor cranial nerve paralysis also categorized as SAEs) were reported in close temporal relationship to vaccination and involve biologically

plausible mechanisms. In addition to inclusion of these events in product labeling (see Section 6.1 in the USPI), this potential safety signal will be addressed via inclusion of “Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)” and as an Important Potential Risk in the pharmacovigilance plan and enhanced pharmacovigilance in postmarketing surveillance. No other new safety concerns were identified.

6.5 Study 313

Study 2019nCoV-313 (Study 313) is a 2-part ongoing Phase 2/3 open-label study evaluating the immunogenicity and safety of a single-dose regimen of the monovalent vaccine (Omicron XBB.1.5) regardless of prior COVID-19 vaccination status in medically stable adults 18 years of age and older.

Study 313 Part 1 was initiated on September 7, 2023 (first participant screened) and completed enrollment on September 8, 2023.

Study 313 Part 2 of the study provides the determinative immunogenicity data that supports the effectiveness of a single dose of the monovalent vaccine (Omicron XBB.1.5) regardless of prior vaccination status. Part 2 was initiated on September 18, 2023, and enrollment was competed on November 15, 2023. An interim analysis of immunogenicity and safety data was conducted at Day 28, with participants remaining on study for immunogenicity and safety data collection up to Day 180 postvaccination. The Applicant submitted a final study report on November 15, 2024 (BLA 125817, Amendment 45) presenting results of primary and secondary endpoints through the last participant, last visit (LPLV) date of May 20, 2024, and data extraction date of July 9, 2024. This review is based upon the final study report.

6.5.1 Objectives

Co-Primary Objectives

To determine if a single dose of the monovalent vaccine (Omicron XBB.1.5) induced noninferior immune responses to the Omicron XBB.1.5 sublineage on Day 28 in seropositive, COVID-19 vaccine-naïve individuals compared with immune responses in participants previously vaccinated with at least 3 doses of an mRNA COVID-19 vaccine (any combination of Pfizer-BioNTech and/or Moderna original monovalent and/or bivalent COVID-19 vaccines) based on the following neutralizing antibody co-primary endpoints:

- Geometric mean titers (GMTs) to Omicron XBB.1.5 subvariant
- Seroresponse rates (SRRs), defined as the percentage of participants with a ≥4-fold rise in antibody response from baseline titers on Day 0

Key Secondary Objectives

- To determine if a single dose of monovalent vaccine (Omicron XBB.1.5) induces superior antibody responses to the XBB.1.5 sublineage compared with baseline titers
    - Endpoints: pseudovirus neutralization titers (ID_{50}) against the Omicron XBB.1.5 sublineage assessed at baseline and at Day 28 postvaccination
- To describe pseudovirus neutralization titers (ID_{50}) to the XBB.1.5 Omicron sublineage induced by the monovalent vaccine (Omicron XBB.1.5)
    - Endpoints: Geometric fold ratio (GMFR) and SRRs at Days 0, 28, and 180
- To assess the overall safety of a single dose of monovalent vaccine (Omicron XBB.1.5)

6.5.2 Design Overview

Study 313 Part 1 was an open-label study that enrolled 332 previously mRNA COVID-19 vaccinated participants. All participants received a single dose of monovalent vaccine (Omicron XBB.1.5) on Day 0, and their immunogenicity and safety data were compared with that of a historical control group of 251 previously mRNA COVID-19 vaccinated participants from Study 311 Part 2 who received a single dose of Novavax Vaccine, Adjuvanted (Original monovalent).

The primary objectives of Study 313 Part 1 were to determine if the monovalent vaccine (Omicron XBB.1.5) induced superior antibody responses in terms of geometric mean titer ratios (GMTR) and noninferior seroresponse rates (SRRs) against the Omicron XBB.1.5 lineage in previously mRNA COVID-19 vaccinated adult participants 18 years of age and older compared with a previously mRNA COVID-19 vaccinated historical control group that received the Novavax Vaccine, Adjuvanted (Original monovalent) in Study 311 Part 2.

A Part 1 interim analysis of primary and secondary endpoints was conducted at Day 28 with a data cutoff date of October 16, 2023 and data extraction date of January 17, 2024, while participants remained on study for immunogenicity and safety data collection up to Day 180 postvaccination. Based on this interim analysis, neutralizing antibody immune responses to the monovalent vaccine (Omicron XBB.1.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron XBB.1.5 pseudovirus met the superiority criterion for the geometric mean titer ratio [GMTR 5.8 (95% CI: 4.85, 6.91), LB of the 95% CI was >1], and met noninferiority criteria for the % difference in SRRs [% difference in SRRs was 57.2% (95% CI: 50.5, 63.2), LB of the 95% CI was >-10%]. As Study 313 Part 1 met superiority and noninferiority success criteria for both GMTR and SRR co-primary immunogenicity endpoints, the previously mRNA COVID-19 vaccinated treatment group that received a single dose of monovalent vaccine (Omicron XBB.1.5) in Part 1 was used as the comparator group for COVID-19 vaccine-naïve participants enrolled in Part 2.

Following completion of Part 1 enrollment, Part 2 was an open-label, single arm study that enrolled 338 vaccine-naïve participants with a clinical history of COVID-19-like disease during the previous year. All participants received a dose of monovalent vaccine (Omicron XBB.1.5) on Day 0. Immune responses on Day 28 after vaccination from these vaccine-naïve participants were then compared with immune responses in the previously mRNA COVID-19 vaccinated participants from Part 1 of the study.

Immunogenicity and 28-day safety data were used for an interim analysis, while participants remained on the study for immunogenicity and safety data collection up to Day 180 postvaccination.

6.5.3 Population

Part 1 of the study enrolled medically stable male and nonpregnant female participants ≥18 years of age 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, who were willing and able to give informed consent prior to study enrollment and to comply with study procedures, and who agreed not to participate in any other SARS-CoV-2 prevention or treatment trials for the duration of the study.

Part 2 enrolled medically stable male and nonpregnant female participants ≥18 years of age who were unvaccinated to SARS-CoV-2 with a medical history of COVID-19-like infection during the previous year. No pre-screening for prior natural infection based on the presence of SARS-CoV-2 nucleocapsid antibodies (anti-N antibodies) was performed before enrollment, however polymerase chain reaction (PCR) for anti-N antibodies was obtained for all enrolled study participants at baseline to confirm prior natural infection, and individuals with a negative anti-N result were excluded from the per protocol analysis. Other eligibility criteria were the same as for Part 1 as described above. See below for inclusion and exclusion criteria and Section 6.5.10.1.1 Demographics for the percentage of participants with positive anti-N antibodies at baseline indicating a PCR-confirmed history of COVID-19 natural infection.

Pertinent exclusion criteria for both Parts 1 and 2 included:

- Autoimmune or immunodeficiency disease/condition (iatrogenic or congenital) requiring ongoing immunomodulatory therapy.
- Chronic administration (defined as >14 days) of immunosuppressant, systemic glucocorticoids, or other immune-modifying drugs within 90 days of study vaccination.

As additional screening criteria, participants who met the following criteria had planned study vaccination deferred for a later date, but these conditions, if transient, were not exclusionary for later study enrollment:

- Respiratory symptoms in the past 3 days (i.e., cough, sore throat, difficulty breathing). Participant could be vaccinated once all symptoms had been resolved for >3 days.
- Temperature of >38°C within 24 hours of planned study vaccination (site measured or participant measured). Participant could be vaccinated once the fever had resolved and there had not been any temperature measured as being >38°C for >3 days. Out-of-window study vaccination was allowed for this reason (see NOTE).
    - Note: Polymerase chain reaction (PCR) testing for SARS-CoV-2 was likely to be indicated for either of the above reasons or if COVID-19 was suspected based on other symptoms, potential exposure to SARS-CoV-2 infection through either close contacts or based on local epidemiology.
- Any participant who was otherwise eligible with a blood pressure (BP) of ≥160/100 mmHg. If the BP remained ≥160/100 mmHg on retesting, study vaccination was deferred for a later date if, at that time, the baseline BP was found to be <160/100 mmHg.
- Participants found to be SARS-CoV-2 positive during the study may be excluded from some analyses as per the SAP but will not be excluded from participation in the study.

Clinical Reviewer Comment: The Applicant's decision not to conduct pre-screening for seropositivity of anti-N antibodies prior to enrollment was based on their data showing that >95% of individuals 6 through 11 years of age in the U.S. are seropositive to SARS-CoV-2 and their expectation of the same or a higher percentage of seropositivity in individuals ≥18 years of age. This approach allowed for the majority of the study population to be included in the primary analysis, as 93.2% of participants had a baseline seropositive anti-N result confirming prior COVID-19 natural infection and only 6.8% were excluded from the primary analysis because they were anti-N negative at baseline.

6.5.4 Study Treatments or Agents Mandated by the Protocol

The study treatment was NVX-CoV2601 monovalent vaccine (Omicron XBB.1.5), a Matrix-M-adjuvanted, SARS-CoV-2 recombinant spike (rS) protein-based COVID-19 vaccine, containing 5 µg of SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered as a single intramuscular injection.

Monovalent (Omicron XBB.1.5) (5 µg): 0.5 mL injection volume at an antigenic dose of 5 µg with 50 µg Matrix-M adjuvant.

6.5.5 Directions for Use

One intramuscular injection of monovalent vaccine (Omicron XBB.1.5) was administered on Day 0.

6.5.6 Sites and Centers

Participants were enrolled at approximately 26 sites in the U.S. and its territories.

6.5.7 Surveillance/Monitoring

Immunogenicity (Laboratory Assays)

Blood samples for immunogenicity assessments were collected and analyzed before vaccination on Day 0 and Day 28 post-single-dose vaccination. To characterize the immune response generated by the study vaccine, blood samples were analyzed for Omicron XBB.1.5 sublineage neutralizing antibody geometric mean titers (GMTs) and seroresponse rates (percentage of participants who achieve ≥4-fold increase in neutralizing antibody titers from baseline on Day 0). Samples were analyzed using validated pseudovirus neutralization assays with an inhibitory dilution of 50% (ID_{50}) to determine Omicron XBB.1.5 sublineage-specific neutralizing antibody titers.

Safety Monitoring

Participants remained under observation for at least 15 minutes postvaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants used an eDiary to record reactogenicity (solicited local injection site and systemic adverse reactions) on the day of vaccination and for an additional 6 days postvaccination.

Unsolicited treatment-emergent AEs (TEAEs) were collected through Day 28 postvaccination

Collection of treatment-related medically attended adverse events (MAAEs), adverse event of special interest (AESIs), and serious adverse events (SAEs) were planned through 6 months postvaccination.

AESIs included potential immune-mediated medical condition (PIMMCs) and complications of COVID-19, including myocarditis/pericarditis. Confirmed symptomatic cases of COVID-19 were recorded as adverse events, SAEs, or AESIs as appropriate.

Scheduled study visits occurred at screening, and Days 0, 28, 90, and 180. Vital sign measurements and physical exam findings were reported at screening, Day 0, and Day 180 (6 months).

6.5.8 Endpoints and Criteria for Study Success

Immunogenicity Endpoints:

The following prespecified success criteria were applied to the co-primary endpoints (described in Section 6.5.1 Objectives) for the monovalent vaccine (Omicron XBB.1.5):

- Noninferiority of monovalent vaccine (Omicron XBB.1.5) neutralizing antibody GMTs against the Omicron XBB.1.5 sublineage in vaccine-naïve participants compared with those in previously COVID-19 mRNA vaccinated participants. Criterion for noninferiority is met if the lower bound of 2-sided 95% CI for GMTR in COVID-19 vaccine-naïve participants versus previously COVID-19 mRNA vaccinated participants is >0.67.
- Noninferiority of monovalent vaccine (Omicron XBB.1.5) SRRs in vaccine-naïve participants compared with previously COVID-19 mRNA vaccinated participants by percentage difference of SRRs for neutralizing antibodies against the Omicron XBB.1.5 sublineage. Criterion for noninferiority by the percentage difference in SRRs is met if the lower bound of the two-sided 95% CI of the estimated percentage difference in SRRs (COVID-19 vaccine-naïve participants minus previously COVID-19 mRNA vaccinated participants) is greater than -10%.

6.5.9 Statistical Considerations & Statistical Analysis Plan

Please see above Section 6.5.8 on Immunogenicity Endpoints for immunogenicity statistical analysis plan.

AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using System Organ Class (SOC) and Preferred Term (PT) according to MedDRA.

6.5.10 Study Population and Disposition

Immunogenicity and safety data through Day 180 were from participants enrolled in the study from the start date of September 18, 2023 (first participant screened) through the date of May 20, 2024, with a data extraction date of July 9, 2024.

6.5.10.1 Populations Enrolled/Analyzed

- Full Analysis Set: all participants who were enrolled and received 1 dose of study vaccine, regardless of protocol violations or missing data (a total of 670 participants in the COVID-19 vaccine-naïve and previously COVID-19 mRNA vaccinated historical control treatment groups).
- Immunogenicity population: all enrolled participants who received the study vaccine according to protocol, had no major protocol deviations or an event (e.g., COVID-1 infection) that was considered clinically relevant to impact immunogenicity responses, and who completed the study blood tests.
- The Per-Protocol (PP) Analysis Set included all participants in the immunogenicity population who tested positive by serologic testing for anti-N antibodies at baseline, tested negative for active SARS-CoV2 infection by PCR at baseline, and completed the study blood tests on Day 28 (a total of 306 COVID-19 vaccine-naïve participants on Day 28).
- Safety population: all enrolled participants who received 1 dose of study vaccine through the data cutoff date of December 19, 2023. Of the 670 enrolled participants, all received a study vaccine and were included in the Safety Analysis Set.

6.5.10.1.1 Demographics

The following table displays a summary of participant demographics and baseline disease characteristics in the Study 313 Part 2 Safety Analysis Set, which includes the COVID-19 vaccine-naïve group in Part 2 of the study along with the previously COVID-19 mRNA vaccinated comparator group from Part 1 of the study, which had been conducted 2 weeks prior to Part 2 of the study.

Table 99. Participant Demographics and Baseline Disease Characteristics, Safety Analysis Set, Study 313

Characteristic	Part 2: COVID-19 Vaccine Naïve Participants – Single Dose Monovalent (Omicron XBB.1.5)[a] N=338	Part 1: COVID-19 mRNA Vaccinated Participants – Monovalent (Omicron XBB.1.5) Booster[b] N=332
Age, years	--	--
Mean (SD)	40.5 (13.11)	52.0 (16.07)
Median	38.0	53.0
Minimum – maximum	18 – 75	18 – 89
Age (years) category, n (%)	--	--
18 through 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)
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	29.80
Minimum – maximum	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[c], n (%)	--	--
Yes	335 (99.1)	5 (1.5)

Characteristic	Part 2: COVID-19 Vaccine Naïve Participants – Single Dose Monovalent (Omicron XBB.1.5)[a] N=338	Part 1: COVID-19 mRNA Vaccinated Participants – Monovalent (Omicron XBB.1.5) Booster[b] N=332
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)[d]	327 (98.5)[e]
Anti-N / PCR[f], n (%)	--	--
Positive	315 (93.2)	234 (70.5)
Negative	23 (6.8)	98 (29.5)

Source: Study 313 Part 2 Final CSR, Table 15
Abbreviations: anti-N=anti-nucleocapsid; BMI=body mass index; COVID-19=coronavirus disease 2019; PCR=polymerase chain reaction; SD=standard deviation.
a. Data for Part 2 were derived from the final analysis.
b. Data for Part 1 were derived from the Day 28 analysis (Table 8 and Table 14.1.5.2 of the 2019nCoV-313 Part 1 Interim Analysis [Version 1.0, dated March 29, 2024]).
c. Previous COVID-19 was derived from programmatically checking Medical History records.
d. 5 participants with missing PCR at baseline were imputed as negative.
e. 2 participants with missing PCR at baseline were imputed as negative.
f. Participants with either anti-N or PCR were reported. Note: Age calculated at time of informed consent.
Note: n for continuous parameters represents the number of participants with non-missing values for that parameter.

In the Safety Analysis Set, demographic characteristics between the groups were relatively balanced for sex, ethnicity, and body mass index (BMI), but there were notable differences in terms of age, race, and history of prior COVID-19 infection. The majority of participants in both the Part 2 vaccine-naive and Part 1 previously COVID-19 mRNA vaccinated historical control groups were female (56.2% and 62.7%, respectively), of non-Hispanic or Latino ethnicity (73.7% and 78.6%, respectively), and either overweight or obese (74.8% and 77.4%, respectively). Vaccine-naïve participants were generally younger (median age 38.0, range 18 to 75 years) than previously COVID-19 mRNA vaccinated participants in the historical control group (median age 53.0, range 18-89 years). Black or African American participants comprised 43.5% of the vaccine-naïve group compared with 16.0% of the historical control group, while roughly half of the participants in the vaccine-naïve group were White (49.4%) compared with a majority of the historical control group (74.7%). Although few participants in the previously COVID-19 mRNA vaccinated historical control group reported a history of COVID-19 infection (1.5%) compared with most participants in the vaccine-naïve group (99.1%), the majority of historical control participants (70.5%) and vaccine-naïve participants (93.2%) were anti-N/polymerase chain reaction (PCR) positive at screening indicating a history of prior natural infection. Five participants in each group (1.5%) were PCR positive at baseline.

Clinical Reviewer Comment: While differences in age and race are noted between Part 1 and Part 2 of this study, none of these differences would be expected to affect the primary outcomes of safety and immunogenicity. Both Part 1 and Part 2 of the study have demographic compositions that are reasonably generalizable to the overall U.S. population, with Part 2 of the study appropriately reflecting disparities in vaccine uptake among Black or African American individuals compared with White individuals. By design, Part 2 participants were enrolled based on a prior history of COVID-19, and 99.1% had medical history records indicating prior COVID-19-like disease. Even though the majority of historical controls in Part 1 reported no evidence of clinical disease, 70.5% of them showed serologic evidence of prior SARS-CoV-2 infection.

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All participants enrolled in the study were medically stable with no autoimmune or immunodeficiency conditions requiring ongoing immunomodulatory therapy.

6.5.10.1.3 Participant Disposition

Of the 419 COVID-19 vaccine-naïve individuals screened in Part 2 of the study, there were 81 screen failures, 338 were enrolled to receive vaccination, 284 (84.0%) completed the study, and early discontinuation occurred in 54 (16.0%) participants. These discontinuations included 40 (11.8%) participants lost to follow-up, 9 (2.7%) participants who decided to withdraw, 2 (0.6%) participants who withdrew due to investigator decision, and 2 (0.6%) participant who withdrew for other reason(s). No participants withdrew from the study due to an adverse event.

Of the 380 previously COVID-19 mRNA vaccinated individuals screened in the historical control group from Part 1 of the study, there were 48 screen failures, 332 were enrolled to receive study vaccination, 329 (99.1%) remained in follow-up at the time of the Day 28 interim analysis, and 3 participants (0.9%) discontinued study participation due to withdrawal by participant.

The full analysis set was comprised of participants who received 1 dose of study vaccine, regardless of protocol violations or missing data, including 338 COVID-19 vaccine-naïve participants and 332 previously COVID-19 mRNA vaccinated participants who received the monovalent vaccine (Omicron XBB.1.5).

> *Clinical Reviewer Comment: A total of 81 participants were considered screen failures, with 73 participants failing to meet inclusion/ exclusion criteria. Even though there were more screening failures in Part 2 than Part 1, this did not result in an underpowered noninferiority analysis, and the final enrolled sample sizes for Parts 1 and 2 were balanced. Although more individuals discontinued study participation in Part 2 than Part 1, this did not have a substantial impact on the safety and immunogenicity results of this study. Furthermore, the higher discontinuation rate is not unexpected given that the study population in Part 2 had declined COVID-19 vaccination prior to enrolling in this clinical trial.*

6.5.11 Immunogenicity Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

Analyses of Primary Endpoint(s)

The table below presents the prespecified co-primary endpoints and success criteria for neutralizing antibody GMT and SRR responses against the Omicron XBB.1.5 pseudovirus generated by the monovalent vaccine (Omicron XBB.1.5) in vaccine-naïve participants from Study 313 Part 2 compared with previously mRNA COVID-19 vaccinated participants from Study 313 Part 1 for the PP Analysis Set on Day 28 postvaccination. The immunogenicity analyses of the two co-primary endpoints for the monovalent vaccine (Omicron XBB.1.5) show that a single dose of the monovalent vaccine (Omicron XBB.1.5) met noninferiority success criteria for both GMTR and the percentage difference in SRRs when comparing immune responses in vaccine-naïve participants with those in previously vaccinated participants.

Table 100. Serum Neutralizing Antibody Titers of Previously COVID-19 mRNA Vaccinated Participants (PP Pseudovirus Neutralization Assay Novavax Clinical Immunology Subset) Against the Omicron XBB.1.5 Subvariant Pseudovirus Following Single Dose Vaccination With Monovalent (Omicron XBB.1.5) in COVID-19 Vaccine-Naïve Participants Compared with Monovalent (Omicron XBB.1.5) Booster, Study 313

Parameter	Part 2: COVID-19 Vaccine-Naïve Participants Single Dose Omicron XBB.1.5 Vaccine N=306	Part 1: COVID-19 mRNA Vaccinated Participants Single Dose Omicron XBB.1.5 Vaccine N=309
Day 0 (baseline)[a]	--	--
n1	288	305
Median	21.0	91.0
Minimum-maximum	21-21647	21.0-33755.0
GMT (ID_{50})	**67.6**	**120.8**
95% CI[b]	56.8, 80.4	101.5, 143.8
Day 28	--	--
n1	288	305
Median	**1506.0**	**970.0**
Minimum-maximum	21-62981	21.0-55900.0
GMT (ID_{50})	**1303.7**	**955.5**
95% CI	**1087.4, 1563.0**	**814.0, 1121.4**
Adjusted GMT (ID_{50})[a]	1491.5	841.4
95% CI	1277.5, 1741.4	723.9, 978.0
GMFR referencing Day 0	19.3	7.9
95% CI	15.7, 23.7	6.8, 9.2
p-value[b]	<0.001	<0.001
Fold increase, n2/n1 (%)	74.3	64.3
95% CI[b]	68.9, 79.3	58.6, 69.6
Comparison between groups	Part 2 vs Part 1	--
GMTR[a]	1.8	--
95% CI	1.4[d], 2.2	--
Difference in SRR[c]	10.0	--
95% CI	2.6[e], 17.4	--

Source: Table 9 of the 2019nCoV-313 Part 2 Interim Analysis (Version 1.0, dated July 17, 2024)
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; COVID-19=coronavirus disease 2019; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups;
ID_{50}=inhibitory dilution of 50%; LB=lower bound; LLOQ=lower limit of quantitation; max=maximum; min=minimum; mRNA=messenger ribonucleic acid; N=number of participants in the assay-specific PP-IMM Analysis Set; n1=number of participants in the assay-specific PP-IMM Analysis Set with non-missing data at both Baseline and Day 28 for this strain; n2=number of participants who reported ≥4-fold increase with percentages calculated based on n1 as the denominator; PP=Per-Protocol; SRR=seroresponse rate
a. An ANCOVA with vaccine group as fixed effect and baseline value (Day 0) as covariate was performed to estimate the adjusted GMT and GMTR. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of GMTs and the corresponding 95% CIs.
b. Two-sided p-value from a paired t-test performed to compare the Day 28 titers with baseline titers.
c. 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.
d. Noninferiority was met for the LB of the two-sided 95% CI for the GMTR exceeded 0.67.
e. Noninferiority was met for the LB of the two-sided 95% CI for the SRR difference was >-10%. Notes: Baseline was defined as the last non-missing assessment prior to vaccination.
Values less than LLOQ were replaced by 0.5 × LLOQ.

Based on the table above, the following neutralizing antibody responses were generated by the monovalent vaccine (Omicron XBB.1.5) in vaccine-naïve participants in Study 313 Part 2 versus previously mRNA COVID-19 vaccinated participants from Study 313 Part 1 against the Omicron XBB.1.5 pseudovirus on Day 28 postvaccination:

Monovalent Vaccine (Omicron XBB.1.5) Primary Analysis:

The estimated GMTR of the monovalent vaccine (Omicron XBB.1.5) in vaccine-naïve participants versus previously mRNA COVID-19 vaccinated participants against the Omicron XBB.1.5 pseudovirus was 1.8 (95% CI: 1.4, 2.2), which met the noninferiority criterion (i.e., the lower limit of the 95% CI around the GMTR is >0.67).

The estimated percentage difference in SRRs of the monovalent vaccine (Omicron XBB.1.5) in vaccine-naïve participants minus previously mRNA COVID-19 vaccinated participants against the Omicron XBB.1.5 pseudovirus was 10.0% (95% CI: 2.6, 17.4), which met the noninferiority criterion (i.e., the lower limit of the 95% CI around the percentage difference in SRRs is >-10%).

> *Clinical Reviewer Comment: The robust immune response induced by a single dose in COVID-19 vaccine-naïve participants likely reflects the rate of prior natural infection with COVID-19 in this population. Vaccine-naïve participants may have experienced "natural priming" from exposure to SARS-CoV-2 Omicron subvariants closer in lineage to circulating XBB.1.5 than previously vaccinated participants who were primed against the ancestral (Wuhan) strain. Despite this limitation in study design, these results support the effectiveness of a single dose of an updated monovalent vaccine in adults 18 years of age and older with presumed pre-existing exposures to SARS-CoV-2, regardless of prior vaccination status.*

Post Hoc Noninferiority Analyses of Study 301 Compared With Study 313

In May 2023, CBER requested that the Applicant conduct a post hoc analysis of immunogenicity data post-dose 1 from Study 301 to evaluate the effectiveness of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the unvaccinated, baseline seropositive population of 792 individuals. The analysis was conducted using a validated Monogram pseudovirus neutralization assay to assess post-dose immune responses. The post hoc, descriptive, noninferiority analysis of the immune responses, as measured by GMT ratios and percentage difference in SCR, induced by Original monovalent vaccine in baseline seropositive individuals 21 days post-dose 1 compared with baseline seronegative adults 35 days post-dose 2 against the ancestral (Wuhan-Hu-1) strain did not meet the >0.67 lower bound of the 95% confidence intervals that would have been necessary to demonstrate noninferiority based on the GMT ratio in participants 12 years and older [GMTR 0.61 (95% CIs: (0.54, 0.68)]. Noninferiority criteria, analyzed descriptively, also did not meet the >-10.0% expected lower bound of the 95% CIs that would have been necessary to demonstrate noninferiority based on the percentage difference in SCRs in participants 12 years and older [% difference in SCR -12.0% (95% CIs: (-14.7, -9.3)]. Based on these results submitted in August 2023, CBER concluded that there was insufficient evidence to demonstrate that single dose of Novavax COVID-19 Vaccine, Adjuvanted in COVID-19 vaccine-naïve seropositive individuals restores effectiveness in protection against circulating SARS-CoV-2 variants and that a 2-dose regimen would be required in these individuals.

The Applicant adapted Study 313 to conduct a prespecified noninferiority analysis comparing the GMTs and SRRs of previously vaccinated individuals and baseline seropositive vaccine naïve individuals, which met noninferiority criteria for success (see Section 6.5), thereby demonstrating the effectiveness of a single dose of Novavax COVID-19 Vaccine (Adjuvanted) in seropositive, COVID-19 vaccine-naïve individuals. The final study report for Study 313 Part 2 became available in October of 2024, post August 2024 authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) to be administered as a 2-dose regimen in COVID-

19 vaccine-naïve individuals and 1-dose regimen in previously COVID-19 vaccinated individuals. When submitted to CBER on December 9, 2024 (IND 22430, SN 703), it was reviewed as part of this BLA.

> *Clinical Reviewer Comment: The success of the noninferiority analysis in Study 313 part 2 may be explained by the exposure of the U.S population to multiple subvariants of SARS-CoV-2 virus [e.g., Alpha, Delta, Omicron,XBB.1.5,], and were primed to generate more robust immune responses after single-dose vaccination at the time of Study 313 enrollment compared with the timing of Study 301 in 2020, when much of the U.S. population may have only been exposed to Wuhan-Hu-1 isolate of SARS-CoV-2.*

6.5.11.2 Analyses of Secondary Endpoints

Secondary immunogenicity endpoint analyses included descriptive analyses of neutralizing antibody responses evaluated separately by age group (18 through 54 years of age, ≥55 years of age). The following sections provide this subgroup analysis by age.

6.5.11.3 Subpopulation Analyses

Following single dose vaccination with monovalent vaccine (Omicron XBB.1.5), GMTs against the Omicron XBB.1.5 pseudovirus were numerically higher in vaccine-naïve older participants ≥55 years of age than in younger participants 18 through 54 years of age at Day 28 [GMT 2009.9 (95% CI: 988.6, 1460.1) vs. 1201.4 (95% CI: 1250.4, 3231.0), respectively] and at Day 180 [GMT 511.0 (95% CI: 323.4, 807.2) vs 277.0 (95% CI: 233.8, 328.1)]. SRRs followed a similar pattern at Day 28 (81.4% vs 73.1%) and Day 180 (55.3% vs 43.2%) in older versus younger vaccine-naïve participants.

> *Clinical Reviewer Comment: The monovalent vaccine (Omicron XBB.1.5) induced neutralizing antibody titers at 1 month that were notably higher in participants ≥55 years of age than in younger participants 18 through 54 years of age, indicating that a single dose of this vaccine is highly immunogenic in older individuals. While the GMT rise, GMFRs, and SRRs are higher in older participants compared with younger participants in general, the fact that the 95% CIs overlapped across the 2 age groups at every time point suggests that the immune responses are comparable across both age groups.*

6.5.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.5.10 on Participant Disposition for a summary of participant discontinuation. There were no participant treatment-emergent adverse events leading to study discontinuation.

6.5.12 Safety Analyses

6.5.12.1 Methods

Please see above Section 6.5.7 on Surveillance/ Monitoring for safety analysis methods.

6.5.12.2 Overview of Adverse Events

Study 313 Part 2 safety data included solicited local AEs, solicited systemic AEs, unsolicited AEs, treatment-related unsolicited AEs through 28 days postvaccination, and safety follow-up for SAEs and AESIs through a median follow-up time of 171 days (approximately 6 months). Part 1 safety data included the same adverse events as Part 2 through a median follow-up time of 173 days.

Solicited Adverse Reactions

The table below presents a summary of solicited local adverse reactions by severity and age in the Safety Analysis Set.

Table 101. Frequency and Percentage of Solicited Local Injection Site Treatment-Emergent Adverse Events Within 7 Days After Single Dose Vaccination with Monovalent (Omicron XBB.1.5) in COVID-19 Vaccine Naïve Adult Participants and Within 7 Days After Monovalent (Omicron XBB.1.5) Booster in Previously COVID-19 mRNA Vaccinated Adult Participants, Safety Analysis Set, Study 313DD

Adverse Event	Part 2 All Participants N=338 n (%)	Part 2 Participants 18 through 54 Years N=284 n (%)	Part 2 Participants ≥55 Years N=54 n (%)	Part 1 All Participants N=332 n (%)	Part 1 Participants 18 Through 54 Years N=176 n (%)	Part 1 Participants ≥55 Years N=156 n (%)
Any solicited local injection site TEAE	--	--	--	--	--	--
Any Grade	140 (41.4)	123 (43.3)	17 (31.5)	189 (56.9)	113 (64.2)	76 (48.7)
≥Grade 3	3 (0.9)	3 (1.1)	0	1 (0.3)	1 (0.6)	0
Pain	--	--	--	--	--	--
Any Grade	85 (25.1)	74 (26.1)	11 (20.4)	98 (29.5)	60 (34.1)	38 (24.4)
≥Grade 3	2 (0.6)	2 (0.7)	0	0	0	0
Tenderness	--	--	--	--	--	--
Any Grade	129 (38.2)	113 (39.8)	16 (29.6)	171 (51.5)	102 (58.0)	69 (44.2)
≥Grade 3	1 (0.3)	3 (1.1)	0	1 (0.3)	1 (0.6)	0
Pain/tenderness	--	--	--	--	--	--
Any Grade	140 (41.4)	123 (43.3)	17 (31.5)	186 (56.0)	112 (63.6)	74 (47.4)
≥Grade 3	3 (0.9)	3 (1.1)	0	1 (0.3)	1 (0.6)	0
Redness	--	--	--	--	--	--
Any Grade	4 (1.2)	3 (1.1)	1 (1.9)	6 (1.8)	2 (1.1)	4 (2.6)
≥Grade 3	0	0	0	0	0	0
Swelling	--	--	--	--	--	--
Any Grade	1 (0.3)	0	1 (1.9)	4 (1.2)	2 (1.1)	2 (1.3)
≥Grade 3	0	0	0	0	0	0

Part 2 Source: Table 14.3.2.1a and Table 14.3.2.1.1a Part 2 Source: Listing 16.2.7.1a and Table 17 of the 2019nCoV-313 Part 1 Interim Analysis (Version 1.0, dated March 29, 2024)
Part 2: COVID-19 Vaccine Naïve Participants Single Dose monovalent vaccine (Omicron XBB.1.5)
Part 1: COVID-19 mRNA Vaccinated Participants Single Dose monovalent vaccine (Omicron XBB.1.5)
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; FDA=United States Food and Drug Administration; mRNA=messenger ribonucleic acid; N=number of participants in the Safety Analysis Set who had any diary data post study vaccination; n=number of participants who reported at least 1 AE; TEAE=treatment-emergent adverse event.
Notes: At each level of participant summarization, a participant was counted once for the most severe grade if the participant reported one or more events.
Maximum toxicity grading is standardized according to the FDA toxicity grading scale: Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Potentially Life Threatening.

As shown in the table above, percentages of local injection site ARs within 7 days postvaccination were generally higher in the previously COVID-19 mRNA vaccinated group from Study 313 Part 1 (56.9%) than in the COVID-19 vaccine-naïve group in Part 2 (41.4%), with a higher percentage in participants 18 through 54 years of age than in participants ≥55 years of age. Pain and tenderness were the most common injection site ARs reported in both groups. Redness and swelling were reported in less than 3% of participants in either group. Grade 3 local solicited ARs were rare (less than 2% of all participants for any event in either group), and no Grade 4 ARs were reported in either group

The median duration of solicited local reactions were similar in both groups. In the vaccine-naïve group in Part 2, the median duration of solicited local injection site ARs was 2.0 days for pain/tenderness and swelling and 1.5 days for redness. Nine participants in Part 2 had solicited local injection site ARs that persisted beyond 7 days (1 participant reported pain/ tenderness of moderate severity lasting up to 74 days).

Pain/ tenderness and redness persisted In the Part 1 previously COVID-19 mRNA vaccinated group, the median duration of solicited local injection site ARs was 2.0 days for pain/tenderness and redness and 1.0 day for swelling. Three participants in Part 1 had solicited local injection site AR persisted beyond 7 days (pain/tenderness lasting up to 9 days).

For Part 2, a higher percentage of solicited systemic TEAEs occurred in younger participants 18 to 54 years of age [140 (49.3%)] compared with individuals >55 years of age [24 (44.4%)]. In general, the percentages of most solicited TEAEs were balanced between the two age groups. However, there was a higher percentage of fatigue in the >55 years of age group [16 (29.6%)] compared with the 18 to 54 years of age group [64 (22.5%)]. Grade 3 solicited AEs were balanced between the two age groups, and there were no Grade 4 AEs.

> *Clinical Reviewer Comment: The percentages of solicited systemic AEs from Study 313 Part 2 are lower than those seen in the pivotal trial for this BLA, Study 301, where overall systemic solicited TEAEs percentage was >70% in participants who completed the initial 2-dose vaccine series. This suggests that reducing the number of initial vaccine doses in COVID-19 vaccine-naive individuals to a single dose may improve the safety profile of this vaccine compared with a 2-dose series.*

Subgroup analyses of solicited ARs were conducted by sex, race, and ethnicity. Solicited ARs in vaccine-naïve participants were reported at slightly higher percentages in female (64.2%) than male (54.1%) participants. No notable differences were observed in the subgroup analyses for race or ethnicity, although many race and ethnicity subgroups had too few participants to draw meaningful conclusions.

Unsolicited Adverse Reactions

The table below presents a summary of frequency and percentage of unsolicited TEAEs in the Safety Analysis Set.

Table 102. Frequency and Percentage of Unsolicited Treatment-Emergent Adverse Events After Single Dose Vaccination With Monovalent (Omicron XBB.1.5) in COVID-19 Vaccine Naïve Participants and After Monovalent (Omicron XBB.1.5) Booster in Previously COVID-19 mRNA Vaccinated Participants, Safety Analysis Set, Study 313

TEAE Categories	Part 2: COVID-19 Vaccine Naïve Participants – Single Dose Monovalent (Omicron XBB.1.5) N=338 n (%); Events	Part 1: COVID-19 mRNA Vaccinated Participants – Monovalent (Omicron XBB.1.5) Booster N=332 n (%); Events
Unsolicited TEAEs reported through 28 days after single dose or booster vaccination	--	--
Any unsolicited TEAE	18 (5.3); 25	30 (9.0); 33
Treatment-related	1 (0.3); 1	4 (1.2); 4
Severe	1 (0.3); 1	2 (0.6); 2
Treatment-related severe	0; 0	0; 0
Any MAAE	8 (2.4); 11	14 (4.2); 15
Severe	1 (0.3); 1	2 (0.6); 2
Unsolicited TEAEs reported through end of study	--	--
Any treatment-related MAAE	0; 0	1 (0.3); 1
Severe	0; 0	0; 0
Serious	0; 0	0; 0
Any SAE	5 (1.5); 5	4 (1.2); 4
Treatment-related	0; 0	0; 0
Any AESIs (PIMMCs)	0; 0	0; 0
Any AESIs: Relevant to COVID-19	0; 0	0; 0
Any myocarditis/pericarditis	0; 0	0; 0
Any TEAE leading to study discontinuation	1 (0.3); 1	0; 0

Source: Study 313 Part 2 Final CSR, Adapted from Table 27 submitted to BLA 125817/0.98
Abbreviations: AE=adverse event; AESI=adverse events of special interest; COVID-19=coronavirus disease 2019; EoS=end of study; Events=number of AEs experienced; MAAE=medically attended adverse event; mRNA=messenger ribonucleic acid; N=number of participants in the Safety Analysis Set; n=unique number of participants experiencing the AE; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), then it was recorded as an AE in the continuing solicited AE form and followed to resolution. Solicited AEs that continued past Day 6 or became SAEs or MAAE were not included in this summary. At each level of participant summarization, a participant was counted once if the participant reported one or more events.
Note: Relationship and severity were based on the data reported by site (i.e., missing information was not imputed).
Related MAAE, Serious TEAE, PIMMC, AESI (COVID-19), myocarditis/pericarditis, and TEAEs leading to any discontinuation are reported through EoS. Other TEAE categories are reported through 28 days after the study vaccination.

Overall, the percentage of unsolicited TEAEs was low (18 [5.3%] for Part 2 and 30 [9.0%] for Part 1). The percentages of treatment related TEAEs, severe unsolicited AEs, unsolicited treatment-emergent MAAEs, severe unsolicited treatment-emergent MAAEs, and serious TEAEs were balanced between Parts 1 and 2. There were no AESIs PIMMCs, AESIs relevant to COVID-19, or cases of myocarditis/pericarditis.

There was 1 TEAE leading to discontinuation involving a fentanyl overdose that resulted in death and is described in Section 6.5.12.3.

Unsolicited severe TEAEs occurred in 1 (0.3%) participant in Part 2 with obstructive pancreatitis and 2 (0.6%) participants in Part 1 (1 with appendiceal abscess and 1 with gastrointestinal

stromal tumor). All 3 events occurred within 28 days after vaccination and were assessed as SAEs that were not related to study vaccine (see SAE narratives below).

Most unsolicited TEAEs in Study 313 were deemed unrelated to study treatment. Six participants experienced unsolicited treatment-related TEAEs: 1 (0.3%) participant in Part 2 (heavy menstrual bleeding) and 5 (1.5%) participants in Part 1 (1 with diarrhea, 1 with axillary pain, 1 with presyncope, 1 with asthma, and 1 with hypertension).

A summary of unsolicited TEAEs by System Organ Class (SOC) and Preferred Term (PT) in the Safety Analysis Set is presented in the table below.

Table 103. Frequency and Percentage of Unsolicited Treatment-Emergent Adverse Events Reported Through 28 Days After Single Dose Vaccination With Monovalent (Omicron XBB.1.5) in COVID-19 Vaccine Naïve Adult Participants and Through 28 Days After Monovalent (Omicron XBB.1.5) Booster in Previously COVID-19 mRNA Vaccinated Adult Participants in >1 Participant, Safety Analysis Set, Study 313

System Organ Class/ Preferred Term	Part 2: COVID-19 Vaccine Naïve Participants – Single Dose Monovalent (Omicron XBB.1.5) N=338 n (%); Events	Part 1: COVID-19 mRNA Vaccinated Participants – Monovalent (Omicron XBB.1.5) Booster N=332 n (%); Events
Any unsolicited TEAE through 28 days after study vaccination	18 (5.3); 25	30 (9.0); 33
Infections and infestations	4 (1.2); 4	12 (3.6); 13
COVID-19	0; 0	5 (1.5); 5
Tooth abscess	0; 0	2 (0.6); 2
Injury, poisoning and procedural complications	3 (0.9); 4	2 (0.6); 2
Respiratory, thoracic, and mediastinal disorders	3 (0.9); 4	4 (1.2); 4
Cough	2 (0.6); 2	2 (0.6); 2
General Disorders and Administration Site Conditions	2 (0.6); 4	3 (0.9); 3
Gastrointestinal disorders	2 (0.6); 2	1 (0.3); 1
Immune system disorders	2 (0.6); 2	0; 0
Psychiatric disorders	2 (0.6); 2	0; 0
Nervous system disorders	1 (0.3); 1	4 (1.2); 4
Migraine	0; 0	2 (0.6); 2
Neoplasm disorders	0; 0	1 (0.3); 1
Blood and lymphatic disorders	0; 0	(0.3); 1
Investigations	0; 0	2 (0.6); 2
Vascular disorders	0; 0	2 (0.6); 2
Hypertension	0; 0	2 (0.6); 2

Part 2 Source: Table 14.3.4.1a Part 2 Source: Listing 16.2.7.3a
Part 1 Source: Table 22 and Table 14.3.4.1 of the 2019nCoV-313 Part 1 Interim Analysis (Version 1.0, dated March 29, 2024)
Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; mRNA=messenger ribonucleic acid; events=number of AEs experienced; MedDRA=Medical Dictionary for Regulatory Activities (version 26.0); N=number of participants in the Safety Analysis Set; n=unique number of participants experiencing the AE; TEAE=treatment-emergent adverse event.

There were 5 (1.5%) cases of COVID-19 postvaccination in the previously COVID-19 mRNA vaccinated participants from Part 1 of Study 313 compared with no COVID-19 cases in vaccine-naïve participants from Part 2. There were otherwise no imbalances seen in specific unsolicited TEAE SOCs and Preferred Terms between the previously COVID-19 mRNA vaccinated participants in Part 1 and the vaccine-naïve participants in Part 2.

By subgroup analysis, unsolicited AEs were balanced between female (7.4%) and male (5.4%) vaccine-naïve participants. While no notable differences were observed in the subgroup analyses for race or ethnicity, many race and ethnicity subgroups had too few participants and/or unsolicited AEs to draw meaningful conclusions.

> *Clinical Reviewer Comment: The unsolicited TEAE data for Study 313 parts 1 and 2 are consistent with the known safety profile of the Novavax COVID-19 vaccine.*

MAAEs

In Part 2 of the study, 8 (2.4%) participants reported at least 1 MAAE through 28 days after single dose vaccination in COVID-19 vaccine naïve adult participants. MAAEs of the SOC Infections and Infestations were the most frequent. Most MAAEs were mild or moderate in severity, with 1 (0.3) participant reporting a severe MAAE of obstructive pancreatitis which was also considered an SAE (see narrative below).

In Part 1 of the study, 14 (4.2%) previously COVID-19 mRNA vaccinated adult participants reported at least 1 MAAE through 28 days after vaccination with Monovalent (Omicron XBB.1.5). The most frequent MAAEs were tooth abscess, migraine, and hypertension. Most MAAEs reported through 28 days after booster vaccination were mild or moderate in severity, with 2 (0.6%) participants reporting severe MAAEs (gastrointestinal stromal tumor and appendiceal abscess, both of which were also SAEs with narratives below).

No MAAEs in Part 2 were assessed as related to study vaccine through 171 days of median safety follow-up. One (0.3%) participant in Part 1 experienced an unsolicited treatment-related TEAE (hypertension) that was also assessed as a treatment-related MAAE through 173 days of median safety follow-up.

Based on subgroup analyses, MAAEs were reported at similar percentages between male and female participants. Subgroup analyses by race and ethnicity were limited due to too few participants with MAAEs in these subgroups for meaningful comparisons. Subgroup analyses of severe MAAEs were of limited value as there were too few participants with severe events.

6.5.12.3 Death

In Part 2 of the study, 1 (0.3%) COVID-19 vaccine-naïve adult participant, a 37-year-old Black or African American female experienced an SAE of fentanyl overdose resulting in death (b) (6) days after receiving the study vaccine after single dose vaccination with monovalent vaccine (Omicron XBB.1.5). The Principal Investigator and Applicant assessed the event of overdose as not related to the study vaccine. This clinical reviewer concurs with their assessment of the event as not related to the study vaccine.

6.5.12.4 Nonfatal Serious Adverse Events

In Part 2 of Study 313, 5 (1.5%) vaccine-naïve participants reported a total of 5 SAEs, with 2 (0.6%) participants reporting cardiac disorders (myocardial infarction), 2 (0.6%) participants reporting gastrointestinal disorders (intestinal obstruction and obstructive pancreatitis), and 1 participant reporting poisoning (overdose) after single dose vaccination with monovalent vaccine (Omicron XBB.1.5). These 5 SAEs were assessed by the investigator and Applicant as not related to study vaccine.

In Part 1 of Study 313, 4 (1.2%) previously COVID-19 mRNA vaccinated adult participants reported a total of 4 SAEs after single dose vaccination with monovalent vaccine (Omicron

XBB.1.5), with 1 participant experiencing gastrointestinal stromal tumor, 1 participant with appendiceal abscess, 1 participant with migraine requiring hospitalization, and 1 participant with ureterolithiasis. These 4 SAEs were assessed by the investigator and Applicant as not related to study vaccine.

> *Clinical Reviewer Comment: The percentage of SAEs was balanced between the vaccine naïve and previously vaccinated participants. Based on an independent review of the narrative information for each reported case, this reviewer concurs with the Investigator that all 9 SAEs were not related to the study vaccine.*

Subgroup analyses of SAEs by age, sex, race, and ethnicity were inconclusive as there were too few participants with serious adverse events.

6.5.12.5 Adverse Events of Special Interest (AESI)

No AESIs were reported.

6.5.12.6 Clinical Test Results

All eligible female participants in Part 2 of the study had negative pregnancy tests at screening.

6.5.12.7 Dropouts and/or Discontinuations

In Part 2 of the study, 1 (0.3%) of 338 participants had a TEAE of fentanyl overdose leading to study discontinuation (participant died; see narrative above in Section 6.5.12.3).

In Part 1 of the study, there was no TEAE leading to study discontinuation after study vaccination through the planned Day 28 interim analysis.

6.5.13 Study Summary and Conclusions

Effectiveness of a single dose of Novavax COVID-19 Vaccine, Adjuvanted in individuals 18 years of age and older regardless of prior COVID-19 vaccination status is inferred from immunogenicity data from Study 313 Part 2 as follows:

- Based on a prespecified immunogenicity analysis, Study 313 demonstrated noninferior neutralizing antibody responses (as measured by GMTR and the percentage difference in SRRs) induced in vaccine-naïve individuals (Part 2) compared with those in previously vaccinated individuals (Part 1) against the Omicron XBB.1.5 sublineage, regardless of prior COVID-19 vaccination status. Data from Study 313 Part 2 support the safety of Novavax COVID-19 Vaccine, Adjuvanted. The safety profiles of a single dose of monovalent (Omicron XBB.1.5), Original monovalent, and bivalent (Original and Omicron BA.5) vaccines in previously COVID-19 vaccine-experienced participants 18 years of age and older were acceptable and comparable to the 2-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

7. INTEGRATED OVERVIEW OF EFFICACY

No Integrated Analysis of Efficacy was provided.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated safety review included Serious Adverse Events (SAEs), Deaths, Significant AEs Leading to Vaccine or Study Discontinuation, and Adverse Events of Special Interest (AESI). SAEs, deaths, significant AEs leading to vaccine or study discontinuation, and AESI were collected from Day 0 to the End of follow-up period.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The Overall ISS Analysis Set contains safety data from participants from Studies 2019nCoV-101 (Part 1), 101 (Part 2), 301 (Adult Main Study and Pediatric Expansion), 302, 307, 311 (Part 1 and Part 2), and 501. Using the Overall ISS Analysis Set, Deaths, nonfatal SAEs, adverse events leading to dropouts and discontinuation, and AESIs were analyzed.

The study design for Studies 301 and 311 (Parts 1 and Parts 2) are described in sections (6.1.2, 6.2.2, 6.3.2, and 6.4.2).

Vaccine manufactured at the (b) (4) scale was considered by FDA as consistent with the commercial product. For three of the early phase studies that are included in the Overall ISS Analysis Set [Studies 101 (Parts 1 and 2), 302, and 501)], vaccine material manufactured at a (b) (4) scale was used. The vaccine that was manufactured using this process was found to non-identical to the commercial product. Because of this, these studies were still considered to be "supportive" and were analyzed in the overall safety database, but they were not used to describe efficacy. The study designs for these three studies are described below:

- Study 101 was a 2-part, Phase 1/ 2 study to evaluate the safety and immunogenicity of a candidate recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant.
    - Part 1 was a Phase 1, first-in-human, observer-blinded, placebo-controlled study conducted in Australia that enrolled healthy adults 18 through 59 years of age with no history of SARS-CoV-2 infection or COVID-19. A total of 134 participants were randomized in a 1:1:1:1:1 ratio to 1 of 5 study groups and received a 2-dose regimen, 21 days apart, of placebo or vaccine at 2 different rS dose levels (5 mcg or 25 mcg of rS antigen) with or without 50mcg of Matrix M adjuvant.
    - Part 2 was a Phase 2, observer-blinded, placebo-controlled study conducted in Australia and the U.S. that enrolled healthy adult participants 18 through 84 years of age with no history of SARS-CoV-2 infection or COVID-19 resulting in medical intervention (mild COVID-19 was allowed). A total of 1,288 participants were randomized in a 1:1:1:1:1 ratio to 1 of 5 vaccine groups to receive different combinations of 5 mcg or 25 mcg of rS antigen with or without Matrix-M adjuvant. Once the dose for licensure was determined to be 5mcg of rS with Matrix-M adjuvant, a subset of participants initially randomized to other formulations were re-randomized to receive 6-month "booster" doses of study vaccine (up to 4 doses of study vaccine overall, including the initial 2-dose series).
- Study 302 was a Phase 3, observer-blinded, placebo-controlled, crossover design study to evaluate the efficacy, safety, and immunogenicity conducted in the United Kingdom that enrolled clinically stable adult participants 18 through 84 years of age with no history

of SARS-CoV-2 infection or COVID-19. A total of 15,185 participants were randomized into the initial vaccination period (pre-crossover). A total of 12,306 (81.0%) completed the study as planned, with 6,237 (82.2%) participants in the NVX-CoV2373 group and 6,069 (79.9%) in the placebo group.

- Study 501 was a Phase 2a/b, observer-blinded, placebo-controlled study conducted in South Africa to evaluate the efficacy, safety, and immunogenicity of Original monovalent vaccine against mild, moderate, or severe COVID-19 in healthy HIV-negative adult participants 18 through 84 years of age and patients living with HIV (PLWH) 18 through 64 years of age. A total of 4,419 participants were randomized 1:1 to vaccine or placebo.
- Study 307 was a Phase 3, observer-blinded, lot-to-lot consistency study comparing the immunogenicity and safety of 3 different lots of NVX-CoV2373 in approximately 900 COVID-19 vaccine-experienced adults 18 through 49 years of age. Participants were randomized 1:1:1 to receive 1 dose of the vaccine from 1 of 3 different lots at a dose level of 5 µg of antigen with 50 µg of Matrix-M adjuvant.

Reviewer Comment: Combining safety data from studies using product made at both scales boosts the potential to detect rare SAEs and AESIs. It is possible that there may be some differences in safety profiles of the vaccines used in the (b) (4) *studies and when compared to the commercial product; however, these vaccines are likely similar enough to justify pooling to generate clinically meaningful integration of safety data.*

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The ISS comprised 31,479 adult and 1,487 adolescent (12 through 17 years old) NVX-CoV2373 recipients and 19,879 adult and 745 adolescent placebo recipients.

Pre-Crossover Vaccination Period

The Overall ISS Analysis Set for the Pre-crossover Primary Series Vaccination Period included all participants who received at least 1 dose of Original Monovalent or placebo on Days 0 and/or 21 of the initial placebo-controlled pre-crossover vaccination period (n=30,070 recipients for the vaccine group and n=19879 recipients for the placebo group). The mean total safety follow-up time since the second vaccine dose during the pre-crossover period was 3.8 (standard deviation 3.02) months.

Post-Crossover Vaccination Period

The Overall ISS Analysis Set for the Post-Crossover Primary Series Vaccination Period pooled safety data from Study 301 and Study 302, which both had similar blinded concurrent control groups and included all participants who received at least 1 dose of Original monovalent or placebo on crossover Days 0 and/or 21 of the blinded post-crossover vaccination period. Participants were analyzed according to the study vaccine they actually received post-crossover (n=9,634 Placebo to Original monovalent recipients and n=18,584 Original monovalent to Placebo recipients). The mean total safety follow-up time since second study vaccination for the Placebo to Original monovalent group was 8.0 months (standard deviation 2.45).

Combined Pre- and Post-Crossover Period

The Pre- and Post-Crossover Primary Series Vaccination Periods were combined for the Overall ISS Analysis Set to provide a pooled analysis of safety events in the Original monovalent recipients compared with placebo recipients during these periods in Study 101 Part 1, Study 101 Part 2, Adult Main Study 301, Study 302, and Study 501. The mean total follow-up time after the second vaccination for this combined Pre- and Post-Crossover Period was 9.0

months (standard deviation 4.22) in the Original monovalent group (N=41,002) compared with 3.5 months (standard deviation 2.46) in the Placebo group (N=19,601).

Clinical Reviewer Comment: When pooling data from the pre- and post-crossover vaccine periods, the 5.5-month difference in mean safety follow-up between the vaccine and placebo groups is notable. This discrepancy illustrates the need to account for the accrual of more safety events with longer safety follow-up in the vaccine group when interpreting pooled safety findings.

Homologous/Heterologous Booster Period

The ISS analysis sets for the Homologous/Heterologous Booster Vaccination Periods included all participants who received 1 booster dose of Original Monovalent (homologous booster after receiving Original Monovalent primary series) or BA.1/ BA.5 monovalent vaccines (heterologous booster after receiving 2 or 3 doses of mRNA vaccine) vaccines in the booster vaccination period and were censored at the day of the second booster vaccination if a participant received 2 booster vaccinations during the booster vaccination period [N=16,945 overall, n=15536 (homologous studies 301, 501, 101 part 2), n=409 (Studies 307 and 311 part 1, heterologous studies with 2 prior mRNA vaccine doses), n=1000 (Studies 307 and 311 part 1 and 2 with ≥3 prior mRNA doses)].

For the Overall ISS Analysis Set, the mean total safety follow-up time since second study vaccination during the homologous/ heterologous booster period for the various study groupings is as follows:

- Studies 101 (Part 2), 301, and 501 - 6.1 months (standard deviation 1.57)
- Studies 307 and 311 (Part 1) NVX-CoV2373 + 2 Prior mRNA Doses – 2.0 months (standard deviation 2.38)
- Studies 307 and 311 (Part 1 and Part 2) NVX-CoV2373 + ≥3 Prior mRNA Doses - 3.0 months (standard deviation 3.32)

The demographic characteristics for the Overall ISS analysis set during the pre-crossover period were balanced between the Original Monovalent and placebo groups. Most participants were 18 through 64 years of age, with 16.5% of participants ≥65 years of age. More than half the participants were male (52.3%), and most participants were White (74.7%) and not of Hispanic or Latino ethnicity (83.5%). Most participants were from the U.S. (56.4%) and U.K. (30.3%). Demographics during the post-crossover period were similar, with the exception of a lower percentage of participants ≥65 years of age (10.8%).

For the Homologous/Heterologous Booster Vaccination Periods, most participants were 18 through 64 years of age, with 11.52% of participants ≥65 years of age in the Overall Analysis Set. More than half the participants were male (50.78%) and not of Hispanic or Latino origin (79.91%). The majority of participants in the Overall Analysis set were from the U.S. (78.65%), while the majority in the Supportive Analysis set were from South Africa.

Clinical Reviewer Comment: The safety findings discussed below are unlikely to be attributable to demographic differences because they were balanced across the vaccine and placebo groups. The different intervals of safety follow-up at each safety timepoint (pre-crossover, crossover, and booster vaccination periods) must be accounted for when integrating safety data by pooling events that occurred in multiple studies in different time periods. The Overall ISS Analysis Set addresses this by reporting event rates per 100

person-years (e/100 PY) as means of correcting for differences in the duration of safety-follow-up between study arms (i.e., vaccine versus placebo).

8.2.3 Categorization of Adverse Events

Version 25.0 of the MedDRA coding dictionary was used for all studies in the ISS.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Differences in study design confounded pooling the safety data during the three safety time points that were reviewed, particularly during the Booster Vaccination Period. Pooling of safety data in the Overall ISS analysis is supported by the similar study design and duration of safety follow-up. Because of the differences in the intervals of safety follow-up, safety events Overall ISS Analysis Set in the were analyzed using event rates per 100 person years (e/100 PY).

8.4 Safety Results

8.4.1 Deaths

Deaths were reported for adult Original monovalent recipients versus placebo recipients who received at least 1 dose of study vaccine during the Pre-Crossover Primary Series Vaccination Period, Post-Crossover Vaccination Period, Combined Pre- and Post-Crossover Vaccination Period, or Homologous/Heterologous Booster Vaccination Period of the pooled studies. Across all periods and studies, the event rates were similar between adults who received Original monovalent and those who received Placebo and are described below. In the Pediatric Expansion of Study 301, no adolescent participant died.

In the Pre-Crossover Primary Series Vaccination Period from Day 0 to end of follow-up for the Overall ISS Analysis Set, a total of 22 participants in the Original Monovalent group and 12 participants in the placebo group died. These numbers translated to similar event rates between Original Monovalent and placebo (0.20 e/100 person-years [PY] and 0.17 e/100 PY, respectively). Event rates of death by demographic characteristics were generally similar between vaccine and placebo groups, except among participants ≥65 years of age (0.50 e/100 PY and 0.38 e/100 PY, respectively), Black or African American (0.56 e/100 PY and 0.40 e/100 PY, respectively), and Other race (0.51 e/100 PY and 0.32 e/100 PY, respectively) participants.

In the post-crossover primary series vaccination period from Day 0 to end of follow-up for the Overall ISS Analysis Set, a total of 11 participants in the Placebo to Original Monovalent group and 32 participants in the Original Monovalent to Placebo group died with similar event rates between the study vaccine groups (0.16 e/100 PY and 0.23 e/100 PY, respectively). Event rates of death by demographic characteristics were generally similar across the study vaccine groups but higher in both the Placebo to Original Monovalent and Original Monovalent to Placebo groups among participants ≥65 years of age (0.28 e/100 PY and 0.59 e/100 PY, respectively) and among Other race participants (0.42 e/100 PY and 0.46 e/100 PY, respectively). Please note that there were 6 deaths from Study 501 that were not included in this analysis. These deaths are accounted for in the combined pre- and post-crossover analysis which is described below.

A total of 71 participants in the Original Monovalent group and 12 participants in the placebo group died during the Combined Pre- and Post-Crossover Vaccination Period, with similar event rates between the study vaccine groups (0.22 e/100 PY and 0.18 e/100 PY, respectively). This included 6 participants in the placebo to Original Monovalent group who were excluded from the Post-Crossover Vaccination Period. Four (<0.01%) deaths in the Original Monovalent group and 3 (0.02%) deaths in the placebo group were reported from Day 0 to Day 21, and 13 (0.03%) and

4 (0.02%) deaths, respectively, were reported from Day 0 to Day 49. The remaining deaths were reported after Day 49. Event rates of death by demographic characteristics were generally similar across the study vaccine groups but higher among participants ≥65 years of age and among Black or African American or Other race participants.

During the Homologous/ Heterologous Booster Vaccination Period for the Overall Analysis Set from Day 0 to End of Follow-Up, a total of 11 participants in the Original Monovalent booster group died, with an event rate of 0.14 e/100 PY, which is comparable to the rates in vaccine and placebo groups from other periods. Event rates of death by demographic characteristics were generally similar across the study vaccine groups but higher among participants ≥65 years of age (0.29 e/100 PY), Black or African American (0.28 e/100 PY), and Other race participants (0.33 e/100 PY). Although across all studies and vaccination periods pooled in the ISS, deaths were reported for 82 adult Original Monovalent recipients and 12 adult placebo recipients, no substantive differences in death event rates between the vaccine and placebo groups were noted. A listing of the deaths that occurred in the ISS are included in Appendix 1. No deaths were attributable to the vaccine.

> *Clinical Reviewer Comment: When studies and vaccination periods (pre-crossover, post-crossover, combined pre- and post-crossover, and booster vaccination periods) are pooled in the ISS, no substantive differences in death event rates between the vaccine and placebo groups were observed. Comparing the gross numbers of deaths does not account for the differences in safety follow-up between the different study groups included in the ISS, and many of these deaths were clearly unrelated to vaccination (car accidents, gunshot wounds, etc.).*

AEs Leading to Death

Pre-Crossover Vaccination Period

The event rates of adverse events leading to death reported in all participants during the pre-crossover vaccination period from Day 0 to End of Follow-up for the Overall ISS Analysis Set were similar among Original Monovalent (0.20 e/100 PY) and placebo (0.15 e/100 PY) groups with a risk difference 0.06 e/100 PY (95% CI -0.07, 0.19). Cardiac AEs leading to death, particularly cardiac arrest, were highest in the pre-crossover primary series vaccination period (0.05 e/100 PY for SOC Cardiac Disorders and Cardiac Arrest compared to 0.04 e/100 PY). Event rates for AEs leading to death were similar among Original Monovalent and Placebo groups.

In the analysis of AEs leading to death, the Preferred Term “death” was reported for cases in which the cause of death was unknown, attributed to natural causes, or included with another Preferred Term denoting a condition that resulted in or contributed to the participant’s death. There were 3 such cases (0.03 e/100 PY) of death in the vaccine group and 0 cases in the placebo group in the Pre-Crossover Period, as shown below in the table of event rates of fatal AEs in the Overall ISS Analysis Set during the Pre-crossover Vaccination Period.

Table 104. Event Rates of Adverse Events Leading to Death Reported in All Participants During the Pre-Crossover Primary Series Vaccination Period (From Day 0 to End of Follow-Up), Overall ISS Analysis Set

System Organ Class/ Preferred Term	Original Monovalent N=30070	Placebo N=19879	Risk Difference (Vaccine – Placebo) e/100 PY (95% CI)
Total follow-up time, PY	11108.1	6890.2	–
Average follow-up time, days	134.9	126.6	–
Median follow-up time, days	104	105	–
Any AE leading to death, n (e/100 PY), (95% CI)	22 (0.20), (0.12, 0.30)	10 (0.15), (0.07, 0.27)	0.06 (-0.07, 0.19)
Cardiac disorders, n (e/100 PY), (95% CI)	5 (0.05), (0.01, 0.11)	4 (0.06), (0.02, 0.15)	-0.02 (-0.10, 0.05)
Cardiac arrest, n (%)	5 (0.05)	3 (0.04)	-0.01 (-0.07, 0.06)
Myocardial infarction, n (%)	0	1 (0.01)	-0.02 (-0.05, 0.02)
General disorders and administration site conditions, n (e/100 PY), (95% CI)	4 (0.04), (0.01, 0.09)	0 (0.00), (NA, 0.05)	0.05 (0.00, 0.09)
Death, n (%)	3 (0.03)	0	0.04 (-0.00, 0.08)
Hanging, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.03)
Injury, poisoning and procedural complications, n (e/100 PY), (95% CI)	4 (0.04), (0.01, 0.09)	0 (0.00), (NA, 0.05)	0.04 (0.00, 0.07)
Gun shot wound, n (%)	2 (0.02)	0	0.02 (-0.01, 0.05)
Accidental overdose, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.02)
Toxicity to various agents, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.02)
Infections and infestations, n (e/100 PY), (95% CI)	3 (0.03), (0.01, 0.08)	3 (0.04), (0.01, 0.13)	-0.01 (-0.07, 0.05)
COVID-19, n (%)	1 (<0.01)	2 (0.03)	-0.02 (-0.06, 0.03)
COVID-19 pneumonia, n (%)	1 (<0.01)	1 (0.01)	-0.01 (-0.04, 0.03)
Septic shock, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.02)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps), n (e/100 PY), (95% CI)	3 (0.03), (0.01, 0.08)	1 (0.01), (0.00, 0.08)	0.02 (-0.03, 0.06)
Cervix carcinoma, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.04)
Colorectal adenoma, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.03)
Metastases to liver, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.03)
Glioblastoma, n (%)	0	1 (0.01)	-0.01 (-0.04, 0.01)
Psychiatric disorders, n (e/100 PY), (95% CI)	2 (0.02), (0.00, 0.07)	2 (0.03), (0.00, 0.10)	-0.00 (-0.05, 0.04)
Completed suicide, n (%)	1 (<0.01)	2 (0.03)	-0.01 (-0.06, 0.03)
Intentional self-injury, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.03)
Nervous system disorders, n (e/100 PY), (95% CI)	1 (<0.01), (0.00, 0.05)	0 (0.00), (NA, 0.05)	0.01 (-0.01, 0.02)
Cerebrovascular accident, n (%)	1 (<0.01)	0	0.01 (-0.01, 0.02)

Source: ISS, Table 121, page 294-295
Abbreviations: AE=adverse event; CI=confidence interval; e/100 PY=event rate per 100 person-years; EOF=End of Follow-up; EUA=Emergency Use Authorization; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); NA=not applicable
Note: Risk difference and its confidence interval were computed from Mantel-Haenszel Standardized Risk Estimates and 95% normal confidence limits with the stratification by study. Note: EOF was defined as date of first crossover or booster dose, date of

last contact, or date of data cutoff for the integrated analysis, whichever was earlier, except for the following scenario: If a participant was unblinded during the Pre-Crossover Primary Series Vaccination Period and received another vaccine approved under EUA, the safety follow-up was censored at the day of unblinding, which was the EOF.
Note: Overall ISS Analysis Set included participants in Clinical Studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301 (Adult Main Study), 2019nCoV-302, and 2019nCoV-501.

Clinical Reviewer Comment: The narratives for these pooled cases of AEs leading to death within the Pre-Crossover Period were reviewed. While there is insufficient information to draw definitive conclusions, it is highly unlikely that these cases represent vaccine-related events that would require additional risk mitigation. These cases are discussed in more detail in the Combined Pre- and Post-crossover analysis below. Event rates were otherwise balanced for the other SAEs leading to death.

Event rates of AEs leading to death by demographic characteristics were generally similar across the study vaccine groups (0.20 e/100 PY for Original Monovalent compared with 0.15 e/100 PY for placebo). The largest difference in event rates between the vaccine and placebo group occurred in females (0.19 e/100 PY in the Original Monovalent group compared with 0.03 e/100 PY in the placebo group), participants ≥65 years of age (0.50 e/100 PY in the Original Monovalent Group compared with 0.28 e/100 PY in the placebo group), Black or African American (0.50 e/100 PY in the Original Monovalent group compared with 0.27 e/100 PY in the placebo group), and Other race participants (0.51 e/100 PY in the Original Monovalent group compared with 0.32 e/100 PY in the placebo group).

Within the Original Monovalent group, AE event rates leading to death were higher in older participants ≥65 years (0.50 e/100 PY) compared with younger participants 18 through 64 years of age (0.13 e/100 PY).

Clinical Reviewer Comment: Event rates for AEs leading to death within the Pre-Crossover Period were low overall (<1 event per 100 person-years). Therefore, the clinical significance of the higher event rate seen in older participants ≥65 years of age (0.50 e/100 PY) compared with younger participants 18 through <65 years of age (0.21 e/100 PY) who received Original Monovalent vaccine during this period is difficult to interpret.

Post-Crossover Vaccination Period

Event rates for AEs leading to death were similar among the placebo to Original Monovalent (0.16 e/100 PY) and Original Monovalent to placebo (0.26 e/100 PY) groups during the Post-Crossover Vaccination Period for the Overall ISS Analysis Set. The individual event rates were generally balanced between the two crossover groups.

There were seven deaths that occurred in the Original Monovalent to Placebo group that were previously addressed in Section 6.1.12.3.

The case of Sudden Death is from Study 302, and the narrative summary is as follows.

- A 51-year-old White male from the United Kingdom with a history of HIV experienced "sudden death" (b) (6) days after receiving the second dose of the Original Monovalent vaccine. The death occurred suddenly, unexpectedly, and outside of the hospital. Information regarding autopsy and death certificate were unavailable; the cause of death was unknown.

The lack of a temporal association between this event and vaccination makes vaccine relatedness unlikely.

Event rates of AEs leading to death by demographic characteristics during the Post-Crossover Period were generally similar between the Placebo to Original Monovalent and Original Monovalent to Placebo study vaccine groups, but AE event rates were higher among participants ≥65 years of age (Placebo to Original Monovalent 0.28 e/100 PY, Original Monovalent to Placebo 0.79 e/100 PY) and Other race participants (Placebo to Original Monovalent 0.42 e/100 PY, Original Monovalent to Placebo 0.55 e/100 PY).

Combined Pre- and Post-Crossover Vaccination Period

Event rates for AEs leading to death were 0.23 e/100 PY among Original Monovalent recipients and 0.15 e/100 PY among placebo groups during the Combined Pre- and Post-Crossover Vaccination Period for the Overall ISS Analysis Set. In general, event rates were low.

There were 13 (0.04 e/100 PY) participants in the vaccine group compared with 0 participants in the placebo group with the preferred term “Death.” Two of these cases were homicides, 7 cases were the deaths from the blinded crossover period from Adult Main Study 301 (see Section 6.1.12.3), and 1 case was a 71-year-old Black or African American female who ultimately died of complications from a CVA (occurred (b) (6) days after vaccination) with concomitant atrial fibrillation. The remaining narrative cases are as follows, with one having temporal association within 30 days of vaccination:

- A 67-year-old Black or African American HIV-negative male from South Africa experienced an SAE of death (b) (6) days after receiving the second initial vaccination. The participant died in his sleep due to natural causes. He was not ill or hospitalized prior to death; a COVID-19 test was not performed.
- A 67-year-old Black or African American HIV-negative female from South Africa experienced an SAE of death (b) (6) days after receiving the second initial vaccination. Her next of kin reported she had been feeling weak and was taken to the clinic a few days prior. She had not experienced any symptoms of COVID-19 and had not been tested for SARS-CoV-2 via PCR. On an unspecified date, an autopsy was performed, and the death certificate listed the cause of death as death due to natural causes.
- An 80-year-old Black or African American HIV-negative female from South Africa experienced an SAE of death (b) (6) days after receiving the second initial vaccination. She missed a visit due to being too weak; she had no symptoms of flu and did not visit any clinic. That night, she died, and it was attributed to natural causes.

Despite insufficient information to draw definitive conclusions, available data do not suggest that these 3 cases represent vaccine-related events that would require additional risk mitigation. In addition, enhanced postmarketing surveillance for atrial fibrillation, myocarditis/ pericarditis, arrhythmia, cardiac failure, cardiomyopathy, and hemorrhagic and non-hemorrhagic stroke will be ongoing.

By subgroup analyses, event rates of AEs leading to death during the Combined Pre- and Post-Crossover Primary Series Vaccination Period were higher in participants ≥65 years of age in the vaccine group (0.60 e/100 PY) compared with Participants 18 to <65 years (0.18 e/100 PY). There were higher percentages of AEs leading to death reported among male participants compared with female participants (0.28 e/100 PY versus 0.18 e/100 PY, respectively). There were higher percentages of AEs leading to death reported among Black or African American and Other race participants (0.38 e/100 PY and 0.55 e/100 PY, respectively) than among participants in other racial groups.

Reviewer Comment: Event rates for AEs leading to death during the Combined Pre- and Post-Crossover Vaccination Period for the Overall ISS Analysis Set were generally low and not suggestive of a safety signal.

Booster Vaccination Period

Event rates for AEs leading to death were 0.17 e/100 PY after homologous booster vaccination with Original Monovalent and 0.00 e/100 PY after heterologous booster vaccination with Original Monovalent during the Homologous/Heterologous Booster Vaccination Period for the Overall ISS Analysis Set. In general, event rates were low and comparable to those seen in the pre- and postvaccination periods. The only AE leading to death that had an event rate of ≥0.05 e/100 PY after booster vaccination was cardiac arrest (0.05 e/100 PY).

By subgroup analyses, event rates of AEs leading to death in the booster period were higher in older participants ≥65 years of age in the vaccine group compared with younger participants 18 through 64 years of age (0.48 e/100 PY versus 0.12 e/100 PY, respectively). There were higher frequencies of AEs leading to death reported among Other race participants than among rest of the subgroups (0.33 e/100 PY).

Clinical Reviewer Comment: Analysis of the Overall ISS Analysis Set did not identify any clustering suggestive of a safety signal among death cases.

8.4.2 Nonfatal Serious Adverse Events

Pre-Crossover Vaccination Period

Event rates of SAEs were similar among Original Monovalent (3.94 e/100 PY) and placebo (3.66 e/100 PY) recipients during the Pre-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set, as shown in the following table.

Table105. Event Rates of Serious Adverse Events in >0.02 e/100 PY in the Original Monovalent Group Reported During the Pre-Crossover Primary Series Vaccination Period (From Day 0 to End of Follow-Up), Overall ISS Analysis Set

System Organ Class/ Preferred Term	Original Monovalent N=30070	Placebo N=19879	Risk Difference (Vaccine – Placebo) e/100 PY, (95% CI)
Total follow-up time, PY	11108.1	6890.2	–
Average follow-up time, days	134.9	126.6	–
Median follow-up time, days	104	105	–
Any SAE, n (e/100 PY), (95% CI)	438 (3.94), (3.58, 4.33)	252 (3.66), (3.22, 4.14)	0.04 (-0.55, 0.63)
Infections and infestations, n (e/100 PY), (95% CI)	71 (0.64), (0.50, 0.81)	54 (0.78), (0.59, 1.02)	-0.20 (-0.46, 0.07)
Appendicitis	8 (0.07)	7 (0.10)	-0.04 (-0.13, 0.05)
COVID-19	6 (0.05)	4 (0.06)	-0.00 (-0.08, 0.07)
Pneumonia	6 (0.05)	7 (0.10)	-0.05 (-0.14, 0.04)
COVID-19 pneumonia	4 (0.04)	9 (0.13)	-0.10 (-0.20, -0.00)
Appendicitis perforated	3 (0.03)	1 (0.01)	0.01 (-0.03, 0.05)
Lower respiratory tract infection	3 (0.03)	1 (0.01)	0.02 (-0.02, 0.06)
Pneumonia aspiration	3 (0.03)	0	0.02 (-0.00, 0.05)
Sepsis	3 (0.03)	2 (0.03)	-0.01 (-0.06, 0.05)

System Organ Class/ Preferred Term	Original Monovalent N=30070	Placebo N=19879	Risk Difference (Vaccine – Placebo) e/100 PY, (95% CI)
Cardiac disorders, n (e/100 PY), (95% CI)	54 (0.49), (0.37, 0.63)	24 (0.35), (0.22, 0.52)	0.09 (-0.11, 0.28)
Atrial fibrillation	10 (0.09)	4 (0.06)	0.02 (-0.06, 0.10)
Acute myocardial infarction	8 (0.07)	3 (0.04)	0.02 (-0.05, 0.10)
Cardiac arrest	6 (0.05)	3 (0.04)	0.00 (-0.07, 0.07)
Acute coronary syndrome	3 (0.03)	0	0.03 (-0.00, 0.06)
Cardiac failure congestive	3 (0.03)	2 (0.03)	-0.01 (-0.06, 0.04)
Myocardial infarction	3 (0.03)	3 (0.04)	-0.02 (-0.08, 0.04)
Injury, poisoning and procedural complications, n (e/100 PY), (95% CI)	52 (0.47), (0.35, 0.61)	29 (0.42), (0.28, 0.60)	0.03 (-0.17, 0.23)
Ankle fracture	5 (0.05)	0	0.05 (0.01, 0.09)
Femur fracture	3 (0.03)	3 (0.04)	-0.01 (-0.07, 0.05)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps), n (e/100 PY), (95% CI)	49 (0.44), (0.33, 0.58)	22 (0.32), (0.20, 0.48)	0.11 (-0.07, 0.30)
Prostate cancer, n (%)	11 (0.10)	1 (0.01)	0.08 (0.02, 0.14)
Breast cancer, n (%)	7 (0.06)	1 (0.01)	0.05 (-0.01, 0.10)
Gastrointestinal disorders, n (e/100 PY), (95% CI)	36 (0.32), (0.23, 0.45)	9 (0.13), (0.06, 0.25)	0.17 (0.04, 0.31)
Gastroesophageal reflux disease, n (%)	3 (0.03)	0	0.03 (-0.00, 0.06)
Obstructive pancreatitis, n (%)	3 (0.03)	1 (0.01)	0.01 (-0.03, 0.06)
Nervous system disorders, n (e/100 PY), (95% CI)	34 (0.31), (0.21, 0.43)	20 (0.29), (0.18, 0.45)	-0.01 (-0.17, 0.16)
Cerebrovascular accident, n (%)	9 (0.08)	3 (0.04)	0.03 (-0.04, 0.10)
Presyncope, n (%)	3 (0.03)	0	0.03 (-0.00, 0.06)
Transient ischemic attack, n (%)	3 (0.03)	1 (0.01)	0.01 (-0.03, 0.05)
Psychiatric disorders, n (e/100 PY), (95% CI)	21 (0.19), (0.12, 0.29)	18 (0.26), (0.15, 0.41)	-0.08 (-0.23, 0.07)
Depression, n (%)	4 (0.04)	2 (0.03)	0.00 (-0.05, 0.05)
Bipolar disorder, n (%)	3 (0.03)	0	0.03 (-0.00, 0.05)
Respiratory, thoracic, and mediastinal disorders, n (e/100 PY), (95% CI)	20 (0.18), (0.11, 0.28)	13 (0.19), (0.10, 0.32)	-0.03 (-0.16, 0.10)
Chronic obstructive pulmonary disease, n (%)	4 (0.04)	1 (0.01)	0.02 (-0.03, 0.06)
Pulmonary embolism, n (%)	4 (0.04)	5 (0.07)	-0.04 (-0.12, 0.03)
Acute respiratory failure, n (%)	3 (0.03)	0	0.02 (-0.00, 0.05)
Asthma, n (%)	3 (0.03)	2 (0.03)	-0.01 (-0.06, 0.05)
Hepatobiliary disorders, n (e/100 PY), (95% CI)	18 (0.16), (0.10, 0.26)	3 (0.04), (0.01, 0.13)	0.10 (0.02, 0.19)
Cholecystitis acute, n (%)	7 (0.06)	0	0.06 (0.01, 0.10)
Cholecystitis, n (%)	4 (0.04)	1 (0.01)	0.02 (-0.03, 0.06)
Cholelithiasis, n (%)	3 (0.03)	0	0.03 (-0.00, 0.05)

System Organ Class/ Preferred Term	Original Monovalent N=30070	Placebo N=19879	Risk Difference (Vaccine – Placebo) e/100 PY, (95% CI)
Renal and urinary disorders, n (e/100 PY), (95% CI)	12 (0.11), (0.06, 0.19)	7 (0.10), (0.04, 0.21)	-0.00 (-0.10, 0.10)
Acute kidney injury, n (%)	9 (0.08)	3 (0.04)	0.03 (-0.04, 0.10)
Vascular disorders, n (e/100 PY), (95% CI)	12 (0.11), (0.06, 0.19)	8 (0.12), (0.05, 0.23)	-0.02 (-0.13, 0.08)
Hypertension, n (%)	3 (0.03)	1 (0.01)	0.01 (-0.03, 0.06)
Hypotension, n (%)	3 (0.03)	1 (0.01)	0.01 (-0.03, 0.05)
Musculoskeletal and connective tissue disorders, n (e/100 PY), (95% CI)	11 (0.10), (0.05, 0.18)	4 (0.06), (0.02, 0.15)	0.03 (-0.05, 0.11)
Intervertebral disc protrusion, n (%)	3 (0.03)	0	0.02 (-0.00, 0.05)
Pregnancy, puerperium, and perinatal conditions, n (e/100 PY), (95% CI)	11 (0.10), (0.05, 0.18)	10 (0.15), (0.07, 0.27)	-0.04 (-0.14, 0.07)
Abortion spontaneous, n (%)	8 (0.07)	3 (0.04)	0.03 (-0.03, 0.10)
General disorders and administration site conditions, n (e/100 PY), (95% CI)	10 (0.09), (0.04, 0.17)	5 (0.07), (0.02, 0.17)	0.01 (-0.08, 0.10)
Death, n (%)	3 (0.03)	0	0.04 (-0.00, 0.08)
Metabolism and nutrition disorders, n (e/100 PY), (95% CI)	8 (0.07), (0.03, 0.14)	13 (0.19), (0.10, 0.32)	-0.12 (-0.24, -0.01)
Dehydration, n (%)	3 (0.03)	3 (0.04)	-0.02 (-0.08, 0.04)
Reproductive system and breast disorders, n (e/100 PY), (95% CI)	5 (0.05), (0.01, 0.11)	4 (0.06), (0.02, 0.15)	-0.01 (-0.09, 0.06)
Blood and lymphatic system disorders, n (e/100 PY), (95% CI)	4 (0.04), (0.01, 0.09)	4 (0.06), (0.02, 0.15)	-0.02 (-0.09, 0.04)

Source: ISS, Table 144, page 341-344
Abbreviations: CI=confidence interval; e/100 PY=event rate per 100 person-years; EOF=End of Follow-up; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities (version 25.0); PY=person-years; SAE=serious adverse event; N=Overall ISS Analysis Set; n=unique number of participants experiencing the adverse event or risk difference in e/100 PY (4th column).
Note: Risk difference and its confidence interval were computed from Mantel-Haenszel Standardized Risk Estimates and 95% normal confidence limits with the stratification by study.
Note: For the Pre-Crossover Primary Series Vaccination Period, the EOF was defined as date of first crossover or booster dose, date of last contact, or date of data cutoff for the integrated analysis, whichever was earlier, except for the following scenario: If a participant was unblinded during Pre-Crossover Primary Series Vaccination Period and received another vaccine approved under EUA, the safety follow-up was censored at the day of unblinding, which was the EOF.
Note: The Overall ISS Analysis Set in the Pre-Crossover Primary Series Vaccination Period included participants in Clinical Studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301 (Adult Main Study), 2019nCoV-302, and 2019nCoV-501.

The highest event rates of SAEs in both study groups were in the SOC Infections and Infestations, and rates were balanced between the Original Monovalent and Placebo groups. Risk differences ≥0.10 e/100 PY were reported for the SOCs Gastrointestinal Disorders (0.17 e/100 PY), Neoplasms, Benign, Malignant and Unspecified (0.11 e/100 PY), and Hepatobiliary Disorders (0.10 e/100 PY). Individual SAEs with an event rate ≥0.10 e/100 PY were prostate cancer (0.10 e/100 PY) among NVX-CoV2373 recipients and COVID-19 pneumonia (0.13 e/100 PY), appendicitis (0.10 e/100 PY), and pneumonia (0.10 e/100 PY) among placebo recipients. No individual SAE resulted in a risk difference ≥0.10 e/100 PY.

Clinical Reviewer Comment: Event rates in atrial fibrillation and cerebrovascular accident were slightly higher in the vaccine group (0.09 e/100 PY and 0.08 e/100 PY, respectively) compared with the placebo group (0.06 e/100 PY and 0.04 e/100 PY, respectively), which was consistent with the safety trends seen in the pivotal study (Study 301).

Event rates were also higher in vaccine group for biliary disease (cholecystitis acute, cholecystitis, cholelithiasis), acute kidney injury, and abortion spontaneous. Acute cholecystitis is addressed in the Section 6 of the EUA Fact Sheet and will be carried forward to the USPI. Nothing further is recommended for biliary disease. For acute kidney injury, the narrative information suggested the acute kidney injury occurred in combination with other diseases such as septic shock or dehydration. This reviewer did not find any further clinical evidence to suggest that acute kidney injury was a potential safety signal. Although event rates of spontaneous abortion were marginally higher in the vaccine group compared with the placebo grout, no statistically significant risk difference was noted for adverse events associated with pregnancy in the overall ISS Analysis Set. Pregnancy-related event rates are difficult to interpret as the studies included in this safety database excluded pregnant women, and data on pregnancies that occurred during safety follow-up are limited. The above data are insufficient to suggest that spontaneous abortion could be a potential safety signal; however, post-marketing surveillance for pregnancy outcomes is ongoing through a pregnancy registry (C-VIPER). Please see Section 9.1.1 for discussion of Human Reproduction and Pregnancy Data.

Results of subgroup analyses by age, sex, race, and ethnicity were similar to those in previous ISS analyses for all subgroups.

Post-Crossover Vaccination Period

SAE event rates >0.02 e/100 PY during the Post-Crossover Vaccination Period for the Overall ISS Analysis Set were similar between the two treatment groups. The 7 “death” cases are addressed in the Adult Main Study 301 section on Death (see Section 6.1.12.3). With regard to subgroup analysis, there was a higher event rate for SAEs occurring in participants ≥65 years of age compared with participants 18 through 64 years of age (Placebo to Original Monovalent 11.18 e/100 PY versus 3.50 e/100 PY, Original Monovalent to Placebo 10.30 e/100 PY versus 3.66 e/100 PY, respectively). The Black or African American and “Other” racial subgroups in the Placebo to Original Monovalent group had slightly higher event rates for SAEs (7.28 e/100 PY and 6.67 e/100 PY, respectively) than the Original Monovalent to Placebo groups (5.74 e/100 PY and 6.20 e/100 PY, respectively) compared with the other racial subgroups. These findings were generally compatible with what was observed in the overall safety population for the pivotal study (i.e., Study 301).

Combined Pre- and Post-Crossover Vaccination Period

SAE event rates >0.02 e/100 PY during the Combined Pre- and Post-Crossover Vaccination Period for the Overall ISS Analysis Set were similar among Original Monovalent (4.17 e/100 PY) and Placebo (3.27 e/100 PY) recipients. Event rates of SAEs of the SOCs Infections and Infestations were the highest in both study vaccine groups, with similar event rates between the 2 groups (0.86 e/100 PY and 0.81 e/100 PY for the Original Monovalent and Placebo groups, respectively). No individual SAE resulted in a risk difference of ≥0.10 e/100 PY.

Results of subgroup analyses by age, sex, race, and ethnicity were similar to those in previous analyses.

The safety trends for atrial fibrillation and cerebrovascular accident SAEs during the Combined Pre- and Post-Crossover Vaccination Period were generally similar to what was observed in the Pre-Crossover Vaccination Period (above). The analysis of the preferred term “Death” was previously addressed in the analysis of the AEs Leading to Death during the Combined Pre- and Post-Crossover Period (above).

Table 106. Event Rates of Serious Adverse Events in >0.02 e/100 PY in the Original Monovalent Group Reported During the Combined Pre- and Post-Crossover Primary Series Vaccination Period (From Day 0 to End of Follow-Up), Overall ISS Analysis Set

System Organ Class/ Preferred Term	Original Monovalent N=41002	Placebo N=19601	Risk Difference (Vaccine – Placebo) e/100 PY, (95% CI)
Total follow-up time, PY	32349.9	6688.2	–
Average follow-up time, days	288.2	124.6	–
Median follow-up time, days	309	105	–
Any SAE, n (e/100 PY), (95% CI)	1348 (4.17), (3.95, 4.40)	249 (3.72), (3.27, 4.22)	-0.28 (-0.82, 0.25)
Infections and infestations, n (e/100 PY), (95% CI)	277 (0.86), (0.76, 0.96)	54 (0.81), (0.61, 1.05)	-0.13 (-0.38, 0.12)
COVID-19 pneumonia, n (%)	37 (0.11)	9 (0.13)	-0.07 (-0.17, 0.04)
COVID-19, n (%)	26 (0.08)	4 (0.06)	0.00 (-0.07, 0.07)
Pneumonia, n (%)	24 (0.07)	7 (0.10)	-0.05 (-0.14, 0.04)
Appendicitis, n (%)	22 (0.07)	7 (0.10)	-0.05 (-0.13, 0.04)
Cellulitis, n (%)	16 (0.05)	1 (0.01)	0.02 (-0.02, 0.06)
Sepsis, n (%)	12 (0.04)	2 (0.03)	-0.01 (-0.06, 0.04)
Cardiac disorders, n (e/100 PY), (95% CI)	154 (0.48), (0.40, 0.56)	24 (0.36), (0.23, 0.53)	-0.01 (-0.18, 0.17)
Atrial fibrillation, n (%)	26 (0.08)	4 (0.06)	-0.01 (-0.07, 0.06)
Acute myocardial infarction, n (%)	25 (0.08)	3 (0.04)	0.03 (-0.04, 0.09)
Myocardial infarction, n (%)	13 (0.04)	3 (0.04)	-0.02 (-0.08, 0.04)
Cardiac failure congestive, n (%)	10 (0.03)	2 (0.03)	-0.01 (-0.06, 0.03)
Coronary artery disease, n (%)	10 (0.03)	0	0.02 (0.01, 0.04)
Cardiac arrest, n (%)	9 (0.03)	3 (0.04)	-0.03 (-0.09, 0.03)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps), n (e/100 PY), (95% CI)	125 (0.39), (0.32, 0.46)	21 (0.31), (0.19, 0.48)	0.07 (-0.08, 0.22)
Prostate cancer, n (%)	21 (0.07)	1 (0.01)	0.05 (0.01, 0.09)
Breast cancer, n (%)	11 (0.03)	1 (0.01)	0.03 (-0.01, 0.06)
Injury, poisoning and procedural complications, n (e/100 PY), (95% CI)	115 (0.36), (0.29, 0.43)	29 (0.43), (0.29, 0.62)	-0.11 (-0.29, 0.07)
Respiratory, thoracic, and mediastinal disorders, n (e/100 PY), (95% CI)	100 (0.31), (0.25, 0.38)	13 (0.19), (0.10, 0.33)	0.02 (-0.10, 0.14)
Pulmonary embolism, n (%)	24 (0.07)	5 (0.07)	-0.02 (-0.09, 0.05)
Chronic obstructive pulmonary disease, n (%)	22 (0.07)	1 (0.01)	0.03 (-0.01, 0.06)
Acute respiratory failure, n (%)	15 (0.05)	0	0.03 (0.01, 0.04)
Nervous system disorders, n (e/100 PY), (95% CI)	93 (0.29), (0.23, 0.35)	19 (0.28), (0.17, 0.44)	-0.04 (-0.18, 0.10)
Cerebrovascular accident, n (%)	17 (0.05)	3 (0.04)	0.00 (-0.05, 0.06)

System Organ Class/ Preferred Term	Original Monovalent N=41002	Placebo N=19601	Risk Difference (Vaccine – Placebo) e/100 PY, (95% CI)
Psychiatric disorders, n (e/100 PY), (95% CI)	88 (0.27), (0.22, 0.34)	17 (0.25), (0.15, 0.41)	-0.04 (-0.18, 0.10)
Suicidal ideation, n (%)	13 (0.04)	4 (0.06)	-0.04 (-0.11, 0.03)
Depression, n (%)	11 (0.03)	1 (0.01)	0.01 (-0.02, 0.04)
Gastrointestinal disorders, n (e/100 PY), (95% CI)	74 (0.23), (0.18, 0.29)	9 (0.13), (0.06, 0.26)	0.06 (-0.05, 0.16)
Hepatobiliary disorders, n (e/100 PY), (95% CI)	54 (0.17), (0.13, 0.22)	3 (0.04), (0.01, 0.13)	0.09 (0.02, 0.16)
Cholecystitis acute, n (%)	18 (0.06)	0	0.04 (0.02, 0.07)
Cholecystitis, n (%)	10 (0.03)	1 (0.01)	0.01 (-0.03, 0.05)
Renal and urinary disorders, n (e/100 PY), (95% CI)	49 (0.15), (0.11, 0.20)	7 (0.10), (0.04, 0.22)	0.01 (-0.08, 0.10)
Acute kidney injury, n (%)	24 (0.07)	3 (0.04)	0.01 (-0.05, 0.07)
Nephrolithiasis, n (%)	11 (0.03)	3 (0.04)	-0.02 (-0.08, 0.04)
Musculoskeletal and connective tissue disorders, n (e/100 PY), (95% CI)	40 (0.12), (0.09, 0.17)	4 (0.06), (0.02, 0.15)	0.04 (-0.03, 0.11)
Osteoarthritis, n (%)	9 (0.03)	1 (0.01)	0.00 (-0.03, 0.04)
Vascular disorders, n (e/100 PY), (95% CI)	37 (0.11), (0.08, 0.16)	8 (0.12), (0.05, 0.24)	-0.04 (-0.14, 0.05)
Deep vein thrombosis, n (%)	10 (0.03)	1 (0.01)	0.01 (-0.03, 0.05)
General disorders and administration site conditions, n (e/100 PY), (95% CI)	34 (0.11), (0.07, 0.15)	5 (0.07), (0.02, 0.17)	0.02 (-0.06, 0.11)
Death, n (%)	13 (0.04)	0	0.06 (0.02, 0.09)
Metabolism and nutrition disorders, n (e/100 PY), (95% CI)	32 (0.10), (0.07, 0.14)	13 (0.19), (0.10, 0.33)	-0.12 (-0.24, -0.00)
Pregnancy, puerperium, and perinatal conditions, n (e/100 PY), (95% CI)	25 (0.08), (0.05, 0.11)	10 (0.15), (0.07, 0.27)	-0.06 (-0.16, 0.04)
Abortion spontaneous, n (%)	19 (0.06)	3 (0.04)	0.03 (-0.03, 0.08)
Reproductive system and breast disorders, n (e/100 PY), (95% CI)	14 (0.04), (0.02, 0.07)	4 (0.06), (0.02, 0.15)	-0.02 (-0.09, 0.05)
Blood and lymphatic system disorders, n (e/100 PY), (95% CI)	9 (0.03), (0.01, 0.05)	4 (0.06), (0.02, 0.15)	-0.04 (-0.10, 0.02)

Source: ISS, Table 163, pages 383-385

Homologous/ Heterologous Booster Vaccination Period

Event rates of SAEs during the Homologous/ Heterologous Booster Vaccination Periods were 4.98 e/100 PY after homologous booster vaccination and 3.05 and 2.05 e/100 PY after heterologous booster vaccinations during the Homologous/Heterologous Booster Vaccination Period in the Overall ISS Analysis Set. Of note, the total follow-up time was highest for the homologous boosting group as compared with the heterologous boosting group with 2 or ≥3 prior mRNA doses (7797.3 PY vs 65.7 PY and 243.6 PY, respectively). Event rates of SAEs in the SOC Infections and Infestations were the highest after primary series and booster vaccination with Original Monovalent vaccine. After homologous booster vaccination, SAEs reported at event rates of ≥0.10 e/100 PY were acute respiratory failure, pneumonia, sepsis, and cellulitis. All these homologous SAE event rates were at or below 0.15 e/100 PY. After heterologous booster vaccination, SAEs reported at event rates of ≥0.10 e/100 PY were gastroenteritis, Escherichia infection, nail bed infection, anaphylactic reaction, endometriosis,

and non-cardiac chest pain. All these heterologous SAE event rates were at or below 0.41 e/100 PY, except for non-cardiac chest pain (1.52 e/100 PY).

No safety signals were identified for non-fatal SAEs in the subgroup analyses of the Heterologous Booster Vaccination Groups in the Overall ISS Analysis Set. Results of subgroup analyses by age, sex, race, and ethnicity were similar to those of the main analysis for all subgroups, excluding those in the 2 heterologous booster vaccination groups. By way of exception, there was a higher percentage of SAEs reported among female participants than among male participants (5.73 e/100 PY compared with 4.26 e/100 PY, respectively). Generally, event rates in other ISS analyses demonstrated similar or higher event rates in males compared to females.

Summary Reviewer Comment: Several of the studies in the ISS were conducted using a vaccine generated from a different manufacturing process than the one used in the pivotal studies (i.e., the (b) (4) studies), which limited the interpretability of these data. Given there were differences in safety follow-up when the studies in the ISS Analysis were combined, analyses were conducted using event rates.

The ISS analyses of deaths did not reveal substantive differences in event rates between the vaccine and placebo groups, suggesting that there was not a safety signal for all-cause mortality. Safety trends for stroke and atrial fibrillation were maintained throughout ISS analyses for SAEs, and this was consistent with findings from the pivotal study (Study 301, Section 6.1.12.4). There were 13 subjects with the preferred term "Death" in the vaccine group compared to 0 in the placebo group, and 10 of these cases contained insufficient information to determine the cause of death. Vaccine relatedness for these 10 cases was unlikely. In conclusion, the ISS safety review did not reveal any new safety signals and provided limited support for atrial fibrillation and CVA as possible safety signals that are being further evaluated with enhanced postmarketing surveillance.

8.4.3 Study Dropouts/Discontinuations

During the Pre-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set, event rates of AEs leading to vaccine discontinuation were similar among Original Monovalent (1.57 e/100 PY) and placebo (1.42 e/100 PY) recipients. Additionally, event rates of vaccine-related AEs leading to vaccine discontinuation were comparable among Original Monovalent (0.35 e/100 PY) and placebo (0.22 e/100 PY) recipients.

Event rates of AEs leading to vaccine discontinuation of the SOCs Nervous System Disorders and General Disorders and Administration Site Conditions had risk differences ≥0.05 e/100 PY (0.08 e/100 PY and 0.05 e/100 PY, respectively), with no individual AEs leading to vaccine discontinuation with risk differences ≥0.05 e/100 PY.

By subgroup analysis, the event rates in the Pre-Crossover Vaccination Period for vaccine discontinuation by age, sex, race, and ethnicity were similar to those of the previous ISS analyses for all subgroups except in participants ≥65 years of age, for whom the rate of AEs leading to discontinuation was slightly elevated in the placebo group compared with the vaccine group (1.69 e/100 PY for the vaccine group versus 4.05 e/100 PY in the Placebo group).

During the Post-Crossover Primary Series, the Overall ISS Analysis Set event rates of AEs leading to vaccine discontinuation were similar among Placebo to Original Monovalent (0.09 e/100 PY) and Original Monovalent to Placebo (0.17 e/100 PY) recipients. No clustering occurred, as all AEs leading to vaccine discontinuation were reported as single events in both

study vaccine groups. Results of subgroup analyses by age, sex, race, and ethnicity were similar to those of the previous ISS analyses for all subgroups. Additionally, event rates of vaccine-related AEs leading to vaccine discontinuation were also similar among Placebo to Original Monovalent (0.03 e/100 PY) and Original Monovalent to Placebo (0.01 e/100 PY) recipients during the Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set.

During the Combined Pre- and Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set, event rates of AEs leading to vaccine discontinuation were 0.60 e/100 PY among Original Monovalent recipients and 1.35 e/100 PY among placebo recipients. Results of subgroup analyses by age, sex, race, and ethnicity were similar to those of the main analysis for all subgroups. Additionally, event rates of vaccine-related AEs leading to vaccine discontinuation were similar among Original Monovalent (0.13 e/100 PY) and placebo (0.22 e/100 PY) recipients during the Combined Pre- and Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set.

During the Booster period there were few AEs leading to study discontinuation, and event rates of AEs leading to study discontinuation were 0.18 e/100 PY, 0.00 e/100 PY and 0.00 e/100 PY in participants who received homologous boosting with Original Monovalent or heterologous boosting with Original Monovalent, respectively in the Overall ISS Analysis Set. These event rates are lower than that reported during the Pre-Crossover Primary Series Vaccination Period and similar to that reported during the Post-Crossover Primary Series Vaccination Period (0.48 e/100 PY and 0.19 e/100 PY, respectively). There were no imbalances or clustering suggestive of a new safety concern.

> *Reviewer Comment: AEs leading to study discontinuation of vaccination or study participation were comparable between Original Monovalent and placebo participants during various periods in the ISS, and there were no imbalances or clustering suggestive of a new safety concern.*

8.4.4 Common Adverse Events

The ISS focused on deaths, nonfatal SAEs, AESIs, and adverse events leading to discontinuation. As not all studies collected solicited adverse events, and as there were no specific imbalances in overall unsolicited AEs that required further evaluation, solicited and unsolicited adverse events were not considered in a pooled fashion. Please see discussions for solicited and unsolicited AEs for Studies 301 (Adult and Pediatric), 311 (Part 1 and Part 2), and 313.

8.4.6 Systemic Adverse Events

See relevant portions of Sections 6.1 and 6.2. Due to the large population size assessed in Study 301, and the use of non-identical product in the (b) (4) studies, systemic and local AEs were not assessed in a combined manner in the ISS.

8.4.7 Local Reactogenicity

See relevant portions of Section 6.1 and 6.2. Due to the large population size assessed in Study 301, and the use of non-identical product in the (b) (4) studies, systemic and local AEs were not assessed in a combined manner in the ISS.

8.4.8 Adverse Events of Special Interest

Potential immune-mediated medical condition (PIMMC)

During the Pre-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set, event rates of PIMMCs were similar among Original Monovalent (0.50 e/100 PY) and placebo (0.54 e/100 PY) recipients during the Pre-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set. Results of subgroup analyses by age, sex, race, and ethnicity were similar to those of previous ISS analyses.

During the Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set, event rates of PIMMCs were higher among placebo to Original Monovalent (0.41 e/100 PY) than among Original Monovalent to placebo (0.26 e/100 PY) recipients. PIMMCs were reported infrequently, and there were no notable imbalances in reported PIMMC between the study arms. Results of subgroup analyses by age, sex, race, and ethnicity were generally similar to those of previous ISS analyses.

During the Combined Pre-and Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set Event rates of PIMMCs were 0.36 e/100 PY among Original Monovalent recipients and 0.54 e/100 PY among placebo recipients. Comparing Original Monovalent and placebo recipients, there were no clustering of PIMMCs suggestive of an association with vaccination. Results of subgroup analyses by age, sex, race, and ethnicity were similar to those of previous ISS analyses.

Event rates of PIMMCs were 0.45 e/100 PY, 0.00 e/100 PY, and 1.23 e/100 PY, respectively, in participants who received homologous boosting with Original Monovalent or heterologous boosting with Original Monovalent in addition to 2 or ≥3 prior mRNA doses during the Homologous/ Heterologous Booster Vaccination Period in the Overall ISS Analysis set. The event rate of 0.45 e/100 PY after homologous booster vaccination was similar to those after primary series vaccination with Original Monovalent during the Pre- and Post-Crossover Primary Series Vaccination Periods (0.50 e/100 PY and 0.41 e/100 PY, respectively).

> *Reviewer Comment: Overall, no new safety signals were identified in the ISS analyses of PIMMCs.*
>
> *Reviewer Comment: Myocarditis is a previously recognized risk for COVID-19 vaccines and for Original Monovalent, and data about events of myocarditis will need to be described in the USPI. The exact association of Original Monovalent with myocarditis can be assessed through active surveillance studies.*

Anaphylactic Reaction

No adult participant reported an SAE of anaphylactic reaction during the Pre-Crossover Primary Series Vaccination Period, Post-Crossover Primary Series Vaccination Period, Combined Pre- or Post-Crossover Primary Series Vaccination Period, or the Homologous/Heterologous Booster Vaccination Period that was attributed to the study vaccine. In the Primary Analysis Set for the Adult Main Study 301, anaphylactic reaction was reported in 1 (<0.1%) participant after receiving booster vaccination with Original Monovalent during the Homologous/ Heterologous Booster Vaccination Period; however, the event was not related to study vaccine but attributed to a pre-existing food allergy.

In addition, no adolescent participant reported an SAE of anaphylactic reaction in the Pediatric Expansion Study 301.

Myocarditis and/or Pericarditis

In the Primary Analysis Set for the Adult Main Study 301, myocarditis was reported in 1 Original Monovalent recipient, myopericarditis in 1 placebo recipient during the Pre-Crossover Primary Series Vaccination Period, and pericarditis in 1 placebo recipient during the Post-Crossover Primary Series Vaccination Period. No participant reported myocarditis, myopericarditis, or pericarditis during the Homologous/ Heterologous Booster Vaccination Period.

In addition, 1 non-serious event of myocarditis and pericarditis was reported in 1 participant during the Post-Crossover Primary Series Vaccination Period. Event rates for myocarditis were similar among Original Monovalent (<0.01 e/100 PY) and placebo (0.01 e/100 PY) recipients, with a risk difference of -0.01 (-0.04, 0.02) during the Combined Pre-and Post-Crossover Primary Series Vaccination Period in the Overall ISS Analysis Set. Event rates for pericarditis and myopericarditis were <0.01 e/100 PY and 0.00 e/100 PY for Original Monovalent recipients and 0.00 e/100 PY and 0.01 e/100 PY for placebo recipients, respectively, with risk differences of 0.01 (-0.00, 0.02) and -0.02 (-0.05, 0.02). No events of myocarditis or pericarditis were reported in participants during the Homologous/Heterologous Booster Vaccination Period in the Overall Analysis Set.

There was 1 additional case of myocarditis and 1 additional case of pericarditis in the vaccine group from Study 302 (a (b) (4) study). There was also 1 case of pericarditis in a placebo recipient from Study 101 part 2 (a (b) (4) study). The total number of myocarditis/ pericarditis cases for the total safety data base is presented in the table below.

Table 107. Total Myocarditis and Pericarditis Cases

Timeframe	Original Monovalent	Placebo
Pre-Crossover Primary Series Vaccination Period	2 (myocarditis)	3 (1 myocarditis + 1 pericarditis + 1 myopericarditis)
Post-Crossover Primary Series Vaccination Period	3 (1 myocarditis/ pericarditis + 2 pericarditis)	0
Homologous/Heterologous Booster Vaccination Period	0	0
Total	5	3

Source: Reviewer Table
All cases occurring at any point after receipt of Original Monovalent, regardless of timeframe, are listed in the Original Monovalent column.

Reviewer Comment: Myocarditis/pericarditis is a previously recognized risk for COVID-19 vaccines and for Original Monovalent, and data about events of myocarditis will need to be described in the USPI. The exact association of Original Monovalent with myocarditis can be assessed through active surveillance studies.

Atrial Fibrillation/ Cerebrovascular Accident/ Myocardial Inflammation

Atrial fibrillation and cerebrovascular accident were previously discussed in section 6.1.12.4. These adverse events were of interest during the safety review of Study 301 because numerical imbalances between the vaccine and placebo group during the pre-crossover period for these two conditions were observed. In addition, the review team observed cases of unexplained death in the overall safety database that were not temporally associated with vaccination and temporally associated cardiac events, including cardiac arrest and myocardial infarction, for which no imbalance was seen in the pre-crossover period. COVID-19 vaccines, including the Original Monovalent vaccine, are known to be associated with myocarditis/ pericarditis. The observation that atrial fibrillation is commonly seen as a complication of myocarditis and

pericarditis suggest a biologically plausible mechanism for a pro-arrhythmic state associated with myocardial inflammation. Because atrial fibrillation is a known risk factor for embolic neurovascular events, there is a biologically plausible mechanism for vaccine relatedness to both temporally associated or potentially more delayed thromboembolic neurovascular events such cerebrovascular accident. The review team recommended adding Atrial Fibrillation to the USPI. In addition, the applicant agreed to enhance post marketing surveillance for both atrial fibrillation, cerebrovascular accident, cardiac failure, and cardiomyopathy.

8.5 Additional Safety Evaluations

A 120-day (4-month) safety update was submitted on July 29, 2024, as an amendment to BLA 125817 containing updated safety information for clinical studies that were ongoing at the time of submission: 2019nCoV-101 Part 2, 2019nCoV-301 (Adult Main), and 2019nCoV-301 (Pediatric Expansion). The submission included a summary assessment of the updated safety information with respect to impact, if any, on the statements of contraindications, warnings, precautions, and adverse reactions in the draft labeling, information related to new deaths, related MAAEs, SAEs, and AESIs that occurred since the time of BLA submission, and narratives and case report forms of any new deaths or AESIs.

Study 101 Part 2

In Study 101 Part 2, 0 deaths occurred, 4 participants reported 4 SAEs, 0 participants reported AESI: PIMMCs, 3 participants reported 3 AESI related to COVID-19, 0 participants reported treatment-related MAAEs. and no participants reported AEs leading to study discontinuation during the period from BLA submission (as submitted in Addendum 1.0 to 2019 nCoV-101 (Part 2) Day 385 CSR) to the final database lock of 12 May 2023.

There was no clustering of SAEs; each of the 4 participants who reported an SAE experienced events in a different SOC. None of the deaths were assessed as related to study vaccine. None of the SAEs reported were assessed as related to study vaccine.

All 3 AESIs related to COVID-19 were in the Cardiac Disorders SOC, and none of the events were assessed as related to study vaccine.

> *Clinical Reviewer Comment: None of the above events were temporally associated with vaccine administration, some events being separated from vaccination by more than a year. This information does not raise a safety concern.*

Adult Main Study 301

In Adult Main Study 301, 22 deaths occurred, 281 participants reported 379 SAEs, 15 participants reported 16 AESI: PIMMCs, 3 participants reported 0 participants reported AESI: PIMMCs, 3 participants reported 3 AESIs related to COVID-19, and 8 participants reported 10 treatment-related MAAEs, and 21 participants reported 24 AEs leading to study discontinuation during the period from BLA submission (as submitted in Addendum 1.0 to the 17-Month Adult CSR) to the final database lock of December 20, 2023. Participants reported these adverse events during the following vaccination periods:

- Pre-Crossover vaccination period: Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
    - Original monovalent: (1 death, 15 SAEs, 1 AESI: PIMMC, 0 AESI: COVID-19, 2 treatment-related MAAEs)

  - Placebo: (2 deaths,12 SAEs, 4 AESI: PIMMCs, 1 AESI: COVID-19, 1 treatment-related MAAE)
- Post-Crossover vaccination period:
  - Placebo to Original monovalent: (0 deaths, 15 SAEs, 0 AESI: PIMMCs, 0 AESI: COVID-19, 1 treatment-related MAAE)
  - Original monovalent to Placebo: (3 deaths, 39 SAEs, 0 AESI: PIMMCs, 2 AESI: COVID-19, 1 treatment-related MAAE)
- Booster vaccination period with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
  - Original monovalent: (16 deaths, 200 SAEs, 10 AESI: PIMMCs).

The distribution of SAE reports in each vaccination period was consistent with the distribution of SAEs reported in the 17-Month Adult CSR. SAEs in the SOC Infections and Infestations were the most frequent. None of the SAEs reported during the Day 120 safety follow-up were considered related to study vaccine, and no new safety concerns were identified.

Most deaths in this 120-day follow-up (16 out of the 22 deaths reported in this study) occurred in the booster period, for which there was no comparator group. None of the deaths were temporally associated with vaccine administration or assessed as related to the study vaccine.

AESIs categorized as PIMMCs included 2 cases of Bell's palsy during the Booster vaccination period that were both assessed as not related to the study vaccine do to a lack of temporal association. All other AESI: PIMMC preferred terms occurred in only 1 participant each, and all were assessed as not related to study vaccine. AESIs related to COVID-19 included 1 case reported in the Renal and Urinary Disorders SOC (description) and 1 case in the Respiratory, Thoracic, and Mediastinal Disorders, and Cardiac Disorders SOC (description). None of the AESIs related to COVID-19 were assessed as related to study vaccine.

None of the treatment-related MAAEs were assessed as serious or considered AESIs.

Of the 21 participants who experienced AEs leading to study discontinuation, 18 cases were fatal AEs. For these 18 deaths, the most frequently reported SOCs were Injury, Poisoning and Procedural Complications (5) and General Disorders and Administration Site Conditions [reported as "Death"] (4)-. None of the AEs leading to study discontinuation were assessed as related to study vaccine.

> *Clinical Reviewer Comment: None of the deaths or AESIs that were reported were temporally associated with vaccine administration. There were 2 participants with acute cholecystitis that were considered serious; however, this Preferred Term is already addressed in the USPI. There was no other clustering of events for SAEs, MAAEs, or adverse events leading to discontinuation to suggest a safety concern.*

Pediatric Expansion Study 301

In Pediatric Expansion Study 301, 0 deaths occurred,19 participants reported 22 SAEs, 1 participant reported 2 AESI: PIMMCs, 0 participants reported AESIs due to COVID-19, 0 participants reported treatment-related MAAEs, and 0 participants reported AEs leading to study discontinuation during the period from BLA submission (as submitted in Addendum 1.0 to the 6-Month Booster Safety Addendum to the 12-Month Adolescent CSR) to the final database lock. These SAEs were reported in participants during the following vaccination periods:

- Post-Crossover vaccination period
    - Placebo to Original monovalent (0 deaths, 0 SAEs, 0 AESI: PIMMC, 0 AESI: COVID-19, 0 treatment-related MAAEs)
    - Original monovalent to Placebo (0 deaths,1 SAE, 0 AESI: PIMMC, 0 AESI: COVID-19, 0 treatment-related MAAEs)
- Booster vaccination period
    - Original monovalent (0 deaths, 18 SAEs, 1 AESI: PIMMCs, 0 AESI: COVID-19, 0 treatment-related MAAEs)

The distribution of SAE reports was consistent with the distribution of SAEs reported in the 6-Month Booster Safety Addendum to the 12-Month Adolescent CSR. SAEs in the SOC Psychiatric Disorders were the most frequent. None of the SAEs reported were assessed as related to study vaccine, and no new safety concerns were identified.

SAEs resulted in death for 18 out of the 19 participants who experienced serious adverse events. There was no observable trend or pattern in the reported deaths, and none of the deaths were assessed as related to the study vaccine.

One participant in the Booster vaccination period reported 2 AESIs categorized as PIMMCs in the SOC Nervous System Disorders. None of the PIMMCs were assessed as related to study vaccine.

Clinical Reviewer Comment: None of the SAEs or AESIs that were reported were temporally associated with vaccine administration. In general, most of the adverse events that were presented in the 120-day (4-month) safety update were not temporally related to vaccine administration, and there was no clustering of events that raised a safety concern. Overall, the 120-day safety update confirmed the safety conclusions for the Novavax COVID-19, Adjuvanted (2024-2025 Formula).

8.6 Safety Conclusions

The ISS analyses evaluated deaths, nonfatal SAEs, AEs leading to discontinuation, common adverse events, and AESIs for the overall ISS population (Studies 301, 307, 311 (parts 1 and 2), 101 (parts 1 and 2), 501, and 302). No new safety signals were identified.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were excluded from enrollment in all clinical studies with Novavax COVID-19, Adjuvanted (Original monovalent). A urine pregnancy test was obtained at screening and prior to each vaccination for study participants of childbearing potential, and individuals with a positive screening test were not administered the study vaccine. Participants were followed for outcomes for all reported pregnancies that occurred after vaccination, and spontaneous abortion was reported as an SAE. A total of 26 pregnancies were reported in Study 301. Unsolicited adverse events reported from day 0 to 49 (28 days post Dose 2) of the pre-crossover period of studies 101 (Part 1), 101 (Part 2), 301, 302, and 501 were reviewed in the

ISS, and no statistically significant risk difference was noted for adverse events associated with pregnancy in the overall ISS Analysis Set (link to Section 8 Integrated Safety Summary).

The Applicant participates in an exposure registry to monitor pregnancy outcomes in women exposed to the Novavax COVID-19 Vaccine, Adjuvanted called C-VIPER (COVID-19 Vaccines International Pregnancy Exposure Registry). This registry has been monitored by the (b) (6) (b) (6) , and no safety signals have been identified. The Applicant also submitted an analysis of their post-authorization safety database using Standardized MedDRA Queries (SMQs) to retrieve individual case safety reports (ICSRs) potentially relevant to pregnant and lactating women, and females and males of reproductive potential (DLP: 31-Jan-2024). For further description of the registry data, the reader is referred to the (b) (6) review memorandum.

Reviewer Comment: Due to the exclusion of pregnant women from trial participation and the limited clinical trial data from participants who became pregnant after vaccination, available data on the Original monovalent vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. A statement conveying the lack of sufficient data on pregnancy and pregnancy outcomes is included in the USPI. While it is reassuring that no safety signals have been identified thus far, the Applicant's commitment to continue an ongoing pregnancy exposure registry study (C-VIPER) to evaluate pregnancy and birth outcomes in individuals exposed to the vaccine during pregnancy may provide additional data to inform the safety profile for use of this vaccine in pregnancy.

9.1.2 Use During Lactation

Breastfeeding women were excluded from participation in all clinical studies with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Novavax did not submit any formal lactation studies in this BLA. Lactation was included in the SMQ analysis that was discussed in Section 9.1.1. Data are not available to assess the effects of the vaccine on breastfed infants or on milk production/ excretion.

9.1.3 Pediatric Use and PREA Considerations

Novavax has addressed their Pediatric Research Equity Act (PREA) requirements for individuals 12 through 17 years of age with Pediatric Expansion Study 301. For further discussion of these data, please see Section 6.2.

To address their PREA requirements, Novavax is conducting ongoing study 2019nCoV-503 (Study 503), a Phase 2/3 age de-escalating study to evaluate the safety and immunogenicity of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in both seropositive and seronegative children for children 6 months through 11 years of age. The immunobridging analysis comparing immune responses of children 2 through 11 years of age to those of young adults 18 through 24 years of age from Pediatric Expansion Study 301 using an ANCOVA model, which accounted for the interaction between age and baseline serostatus, met noninferiority criteria for demonstrating effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in COVID-19 vaccine-naïve children who were seronegative at baseline, but it did not meet noninferiority criteria who were seropositive at baseline. The youngest cohort from study 503 (6 months to <2 years of age) was not included in this immunobridging analysis, as this portion of the study was ongoing at the time of the preliminary analysis. In response to CBER's request for a new study to re-assess the effectiveness of their vaccine in the seropositive pediatric population, Novavax agreed to conduct the following deferred studies in a communication received November 27, 2024:

- Study 2019nCoV-317 to evaluate the immunogenicity of Nuvaxovid in COVID-19 vaccine-naïve seropositive individuals 2 years through <12 years of age and to evaluate the safety and immunogenicity of Nuvaxovid in individuals 6 months through <2 years of age, using a contemporaneously vaccinated comparator group.
- To address their PREA requirements for children 0 through <6 months of age Novavax is conducting Study 2019nCoV-506 to evaluate the safety and immunogenicity of Nuvaxovid in COVID-19 vaccine-naïve individuals.

Reviewer Comment: Specific aspects of the design for both studies will be discussed with the Applicant when the full protocols are submitted for FDA review.

9.1.4 Immunocompromised Patients

Save for Study 501, all other clinical trials submitted to BLA 125817 specifically excluded individuals with autoimmune or immunodeficiency diseases. Study 501 did include participants that were infected with HIV which will be further discussed in Section 9.2. Participants receiving chronic (defined as greater than 14 continuous days) and immunosuppressive dosing levels (greater than 20 mg) of corticosteroids were also excluded. Participants with stable endocrine disorders such as thyroiditis, pancreatitis, and stable diabetes mellitus were not excluded. Because immunocompromised patients were not evaluated, no conclusions can be drawn about the safety and effectiveness of Novavax COVID-19 Vaccine (2024-2025 Formula) in this patient population.

9.1.5 Geriatric Use

In Adult Main Study 301, 13% (n=2,200) of the participants in the Original Monovalent arm and 13% (n=961) participants in the placebo arm were 65 years of age and older. The vaccine efficacy in this age group was 68.0% (95% CI: -43.0, 92.8), which is presented in the table below.

Table 108. Subgroup Analyses of Vaccine Efficacy against PCR-Confirmed Symptomatic Mild, Moderate, or Severe COVID-19 With Onset From at Least 7 Days After Second Vaccination of the Initial Vaccination Period in Serologically Negative Adult Participants, PP-EFF Analysis Set

Age	Original Monovalent Cases[a] n/N (%) (Mean Incidence Rate/1,000 Person-Years)[c]	Placebo Cases[a] n/N (%) (Mean Incidence Rate/1,000 Person-Years)[c]	Vaccine Efficacy[b] (95% CI)
18 to <65 years	15/15162 (0.1) (5.7)	72/7365 (1.0) (61.8)	90.8 (83.9, 94.7)
≥65 years	3/2022 (0.1) (8.6)	4/961 (0.4) (26.8)	68.0 (-43.0, 92.8)
50 to <65 years	4/5525 (0.1) (4.2)	17/2809 (0.6) (39.3)	89.2 (67.9, 96.4)

Source: 2019nCoV-301: Addendum 1.0 to Adult 17 Month CSR Pages 51-54
Abbreviations: CI=confidence interval; COVID-19=coronavirus disease 2019; NP=nucleoprotein; PCR=polymerase chain reaction; RR=relative risk; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2;; VE=vaccine efficacy; N=PPEFF analysis set for Study 301; n=number of unique participants in each category.
a. Case=First occurrence of PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second injection within the surveillance period.
b. VE (%)=100 × (1-RR) in SARS-CoV-2-naive (confirmed seronegative by anti-NP and no active COVID-19 infection by PCR test at baseline) adults who received both doses of trial vaccine (Original Monovalent or placebo) in the initial vaccination period. RR is ratio of incidence rates of active group relative to the placebo group (Original Monovalent/placebo) with first occurrence of case with onset during a surveillance period from 7 days after second injection up to censor date. Participants were censored at the earliest of (i) cut-off date (18 August 2022), (ii) date of major protocol deviation, (iii) date of death, (iv) date of unblinding (including for intended

receipt of alternative COVID-19 vaccine), (v) early withdrawal end of follow-up, or (vi) first dose of blinded crossover. PCR-positive participants who did not meet mild, moderate, or severe COVID-19 criteria were censored at date of the PCR-positive.
c. Rate/1,000 Person-Years

> *Clinical Reviewer Comment: The efficacy of the Original Monovalent vaccine in the geriatric population of ≥65 years of age was lower than younger adults and adolescents. The lower number of cases of COVID-19 and the smaller number of participants who were ≥65 years of age, led to a wider 95% Confidence Interval with a negative lower bound, which limits the interpretability of this result. It is likely that the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1) vaccine in geriatric individuals ≥65 years of age is comparable to younger individuals; however, there is insufficient data from study 301 or Study 311 to draw definitive conclusions. This limitation is addressed in the USPI.*

The safety of the Original Monovalent vaccine is extensively discussed in Section 6.1.12. No safety concerns specific to the geriatric age group were identified. The reported frequencies of adverse reactions, including myocarditis/pericarditis, were generally comparable or lower in the geriatric age group compared with younger adults and adolescents.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered: People Living With Human Immunodeficiency Virus (PLWH)

People living with HIV (PLWH) were evaluated in both Study 301 (n=183 out of 25,519 participants) and Study 501 (n=246 out of 4419 participants). Study 301 did not include prespecified safety analyses in the HIV subgroup; however, these participants were included in the overall Safety Analysis Set. Study 501, on the other hand, did include HIV subgroup analyses that evaluated efficacy, immunogenicity, and safety. Study 501 was conducted using a vaccine made with a different manufacturing process than the commercial formulation.

Study 501

Study 2019nCoV-501 is a Phase 2a/b, randomized, observer-blinded, placebo-controlled trial evaluating the efficacy, immunogenicity, and safety of NVX-CoV2373 in adult healthy HIV-negative participants ≥18 to <85 years of age or medically stable PLWH ≥18 to <65 years of age conducted in South Africa. A minimum of approximately 3,200 to a maximum of approximately 4,404 participants were to be randomized 1:1 to receive up to 2 intramuscular (IM) injections of SARS-CoV-2 rS with Matrix-M adjuvant or placebo in the Initial Vaccination Period.

In Study 501, vaccine efficacy was greater than 70%, but the confidence intervals were wide, and the p-value was not statistically significant. An analysis of IgG antibody levels demonstrated slightly lower GMTs, GMTR, and SRR compared with HIV-negative participants at Days 21 and 35. Adult Main Study 301 had a subgroup efficacy analysis in participants with HIV which was 100%; however, the confidence intervals were wide making it difficult to draw definitive conclusions. These data suggest that Original Monovalent vaccine generated at least comparable immune responses in PLWH when compared with HIV-negative participants. The fact that the vaccine from Study 501 was manufactured using a different process than the authorized Original Monovalent vaccine makes the above data less relevant in supporting the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1) than the subgroup efficacy data in participants with HIV from Adult Main Study 301, which evaluated the formulation.

The safety data from Study 501 suggested that PLWH had comparable percentages of participants reporting solicited, unsolicited treatment emergent, and serious unsolicited

treatment emergent adverse events compared with HIV-negative participants. There were no deaths in the PLWH subgroup.

Adult Main Study 301 Safety Analysis

A reviewer analysis was conducted comparing the PLWH subgroup to the HIV-negative participants in Study 301. In general, there were no imbalances regarding deaths, SAEs, and adverse events leading to discontinuation. There were higher percentages of several SAEs in the PLWH in the vaccine group compared with placebo including headache, nasal congestion, rhinorrhea, diarrhea, myalgia, pain fatigue and cough. There were also higher percentages of these unsolicited adverse events in the vaccinated PLWH subgroup compared with the non-HIV vaccinated subgroup. The interpretability of these analyses was confounded by the low number of participants in the PLWH subgroup (n=172) compared with the non-HIV participants (n=21,497).

In summary, the efficacy data from both Studies 301 and 501 and the immunogenicity data from Study 501 are difficult to interpret, particularly because the vaccine used in Study 501 was manufactured using a different process. However, the available data suggest the Original Monovalent vaccine was likely effective in participants living with PLWH. The safety profile of the Original Monovalent vaccine was comparable or better than what was seen in HIV-negative participants in Study 501.

In addition to the supportive data described above, the effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1) in PLWH 18 years of age and older is extrapolated from the efficacy data in unvaccinated adults from Adult Main Study 301 and the bridging noninferiority immunogenicity analyses from Study 311 parts 1 and 2. The noninferiority analysis from Study 313 Part 2 supports single-dose administration regardless of vaccine history in all adult populations including PLWH.

The safety of the Original Monovalent (Wuhan) vaccine and by extension, the 2024-2025 Formula (JN.1) vaccine in PLWH, 18 years of age and older, was supported by the safety data from Study 501 and Study 301. There were no safety signals or substantial imbalances in the percentages of adverse events seen in this patient population compared with HIV-negative individuals. If the totality of evidence is considered, there is sufficient clinical evidence to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is safe and effective in adults living with HIV.

9.3 Conclusions

Due to the exclusion of pregnant women from trial participation and the limited clinical trial data from participants who became pregnant after vaccination, available data on the Original monovalent vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy and lactation. Novavax will be conducting deferred pediatric studies to further evaluate updated Novavax vaccines in children aged 11 years down to birth. The studies submitted to this BLA were not designed to assess individuals with autoimmune immunodeficiency diseases, save for Study 501 which evaluated PLWH. There were limited data from Study 301 (a descriptive efficacy analysis and limited safety data) for PLWH. Together these data provided some limited evidence for vaccine effectiveness for the Original Monovalent vaccine. The effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1) in PLWH 18 years of age and older is extrapolated from the efficacy data in unvaccinated adults from Adult Main Study 301 and the bridging noninferiority immunogenicity analyses from Study 311 parts 1 and 2. The noninferiority analysis from Study

313 Part 2 supports single-dose administration regardless of vaccine history in adult populations including PLWH. In general, the safety profile of the Original Monovalent Vaccine in PLWH was comparable to or better than HIV-negative participants, and this can be extrapolated to the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1). Finally, there was insufficient evidence to draw definitive conclusions regarding the effectiveness of either the Original Monovalent or the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (JN.1) vaccine in geriatric individuals. The safety profile in geriatric patients is comparable to or better than what is seen in younger individuals.

10. CONCLUSIONS

The data submitted to this BLA provide evidence to support the safety and effectiveness of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, when administered as a single dose (5 µg rS antigen/ 50 µg Matrix-M adjuvant), irrespective of prior COVID-19 vaccination status.

Data supporting effectiveness of a single dose (5/ 50 µg) of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in individuals 12 years of age and older, irrespective of prior COVID-19 vaccination status, include the following:

Efficacy and Effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)

- Individuals 18 years of age and older
  - Efficacy of the Original Monovalent vaccine, given as a 2-dose series in unvaccinated individuals, was demonstrated based on clinical efficacy endpoints from Adult Main Study 301 (reviewed in Section 6.1) and
  - Immunogenicity of the Original Monovalent vaccine, given as a single dose in COVID-19 vaccine-experienced individuals 18 years of age and older, was supported by a noninferiority analysis between the neutralizing antibody responses measured after the second and third doses from Adult Main Study 301 (reviewed in Section 6.1), and
  - Immunogenicity of an updated monovalent vaccine in both COVID-19 vaccine-experienced and vaccine-naive adults was supported by:
    - Noninferiority analyses comparing the neutralizing antibody responses from a single dose of the monovalent Omicron BA.1 and BA.5 vaccines versus the Original Monovalent vaccine in COVID-19 vaccine-experienced populations from Study 311 parts 1 and 2 (reviewed in Sections 6.3 and 6.4).
    - Immunogenicity of updated vaccines administered as a 2-dose series in vaccine-naive population was based on extrapolation from the monovalent Omicron BA.1 and BA.5 noninferiority analysis of a single dose in previously vaccinated adults and the noninferiority immunogenicity analysis that supported a single dose of the Original Monovalent vaccine in previously vaccinated individuals (reviewed in Sections 6.1, 6.3, and 6.4).
  - Immunogenicity of a single dose of an updated monovalent vaccine (Omicron XBB.1.5) regardless of vaccine history, which was supported by a noninferiority analysis of neutralizing antibody responses in previously vaccinated adults compared with vaccine-naïve, baseline seropositive adults from Study 313 parts 1 and 2 (reviewed in Section 6.5).

- Based on the totality of the evidence, namely the clinical efficacy and immunogenicity data from Adult Main Study 301, the descriptive immunogenicity analyses for the monovalent Omicron BA.1 and BA.5 vaccines from Study 311 parts 1 and 2, and the noninferiority analysis supporting a single dose vaccine regimen regardless of vaccine history in adults who received the monovalent vaccine (Omicron XBB.1.5), it was concluded that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) would be effective in individuals 18 years of age and older.

- Individuals 12 through 17 years of age
  - Immunogenicity of the Original Monovalent vaccine, given as a 2-dose series in unvaccinated individuals 12 through 17 years of age, which was supported by comparing neutralizing antibody titers in adolescents 12 through 17 years of age to those of adults, 18 years of age and older, based upon a pre-specified noninferiority endpoint (reviewed in Section 6.2).
  - Immunogenicity of the Original Monovalent vaccine in previously vaccinated individuals 12 through 17 years of age, which was supported by a noninferiority analysis between neutralizing antibody responses measured after the second and third doses from Pediatric Expansion Study 301 (reviewed in Section 6.2).
  - Immunogenicity of an updated monovalent vaccine in both vaccinated and unvaccinated individuals 12 through 17 years of age was extrapolated from a noninferiority analyses in adults comparing the neutralizing antibody responses from a single dose of the Monovalent BA.1 and BA.5 vaccines and the Original Monovalent vaccine in previously vaccinated individuals from Study 311 Parts 1 and 2 (reviewed in Sections 6.3 and 6.4) and previously unvaccinated individuals Study 313 Part 2 (reviewed in Section 6.5).
  - Immunogenicity of a single dose of an updated vaccine (XBB.1.5) regardless of vaccine history in individuals was extrapolated from a noninferiority analysis of neutralizing antibody responses in previously vaccinated adults compared with vaccine naïve, baseline seropositive adults from Study 313 Parts 1 and 2 (reviewed in Section 6.5).
  - Based on the totality of evidence, including the efficacy and immunogenicity data from Pediatric Expansion Study 301, as well as extrapolation from the immunogenicity analyses for the monovalent BA.1 and BA.5 vaccines from Study 311 parts 1 and 2 in adults, and the noninferiority analysis supporting a single-dose vaccine regimen regardless of vaccine history in adults who received the XBB.1.5 vaccine, it was concluded that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) would be effective in individuals 12 through 17 years of age.

Safety of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula)

The Safety of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in both adults and adolescents is supported by the following:

- Individuals 18 years of age and older
  - Adult Main Study 301
    - The available safety analysis population of N=29,582, which included 19,735 recipients of at least one dose of the Original Monovalent and 9,847 placebo recipients during the initial pre-crossover vaccination period.

    - Approvable safety profile with atrial fibrillation, cardiac failure, cardiomyopathy, non-cardiac, non-neurovascular embolic events, uveitis, acute cholecystitis, lymphadenopathy, and myocarditis/ pericarditis addressed in the USPI and appropriate postmarketing surveillance.
  - Study 311 Parts 1 and 2
    - The available safety analysis population of N=1,709, which included 586 recipients of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and 1123 recipients of updated formulations of the vaccine (Omicron BA.1 and Omicron BA.5 monovalent vaccines and bivalent vaccines containing Original monovalent and either Omicron BA.1 or BA.5).
    - Approvable safety profile with oculomotor cranial nerve palsy and vestibular neuronitis addressed in the USPI and in appropriate postmarketing surveillance.
  - Study 313
    - The available safety analysis population of N=670, which included 338 vaccine-naïve and 332 previously COVID-19 vaccinated recipients of monovalent vaccine (Omicron XBB.1.5)
  - Approvable safety profile with no new safety concerns.
- Individuals 12 through 17 years of age, Pediatric Expansion Study 301
  - The available safety analysis population of N=2,232, which included 1,487 recipients of at least one dose of the Original Monovalent and 745 placebo recipients during the initial pre-crossover vaccination period.
  - Approvable safety profile with no additional recommendations for labeling or additional postmarketing surveillance.

Based on the totality of the data submitted to this BLA and the risk-benefit considerations as described in Section 11, the clinical reviewers conclude that the clinical trial data submitted in this application, and complemented by available postmarketing data, support approval of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), administered as a single dose (5/50 µg) for the indication of active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Consideration

Table 109. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for nearly 104 million cases and 1.1 million deaths in the U.S. since the onset of the pandemic in 2020. • There has been a succession of SARS-CoV-2 variants (Delta, Omicron BA.1, BA.5, XBB.1.5, JN.1) with continued evolution of the virus, particularly in the receptor binding domain of the Spike protein. • In vitro immunological assessments of the neutralizing antibody responses against emerging variants show increased neutralization by antibodies induced by updated vaccine formulas in both nonclinical and clinical studies.	• COVID-19 is a serious disease associated with significant morbidity and mortality from acute infection and additional morbidity from post-acute sequelae of COVID-19 (Long COVID) in a subset of individuals with COVID-19. • Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Original monovalent mRNA-based COVID-19 vaccines authorized in the U.S. had high efficacy (90-95%) against symptomatic disease in adequately designed and well-controlled trials conducted early in the COVID-19 pandemic.
Current Options for Treatment or Prevention of COVID-19	• Antiviral medications and monoclonal antibodies have been approved or authorized for the management of individuals with COVID-19; these therapeutics are more effective when taken soon after disease onset. The age of the patient and the presence or absence of hybrid immunity from natural infection and prior COVID-19 immunization may also affect the benefit of using these treatments for COVID-19. • Currently, the 2024-2025 Formula of the mRNA COVID-19 vaccines are available for use in the U.S. for individuals 6 months of age and older. • An adjuvanted, protein subunit COVID-19 vaccine (2024-2025 Formula) is authorized for use in individuals 12 years of age and older.	• Although treatments exist for those infected with SARS-CoV-2, their effectiveness is influenced by the age of the patient, the severity of the disease at the start of treatment, and by prior SARS-CoV-2 infection(s) and prior COVID-19 immunization(S). Treatment effects on post-acute sequelae of COVID-19 (Long COVID) are uncertain. • COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines prevent COVID-19 caused by SARS-CoV-2.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Nonclinical data demonstrating that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), when used in vaccine-naïve or vaccine-experienced laboratory animals, elicited higher neutralizing antibodies against circulating JN.1-related sublineages compared with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). • Residual uncertainty remains in how the magnitude of the expected increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease.	• The totality of the available evidence indicates that the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may provide benefit, particularly against currently circulating JN.1-related sublineages. • Given the enhanced neutralizing antibody activity against more recently circulating SARS-CoV-2 variants demonstrated in nonclinical studies of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) compared with the previously authorized Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) it is reasonable to expect that administration of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may provide additional benefit compared with administration of previous formulas.
Risk and Risk Management	• Additional doses may be associated with transient local and systemic symptoms like those seen with primary series and prior booster doses. • Important risks that are recognized with Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) include myocarditis and/or pericarditis (important identified risk) and ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI) and atrial fibrillation and CVAs (important potential risk).	• Post-deployment monitoring for adverse events using both passive and active surveillance systems will be used to assess whether any new safety concerns emerge.

11.2 Risk-Benefit Summary and Assessment

11.2.1 Known and Potential Benefits

Due to low vaccine uptake, Studies 401 and 403 (post-authorization studies conducted to evaluate vaccine effectiveness) did not provide interpretable data to further inform vaccine effectiveness. Therefore, the post-authorization, Real-World-Evidence of effectiveness of the updated, Nuvaxovid COVID-19 vaccines are unknown. Nonetheless, it is reasonable to expect comparable effectiveness to the effectiveness of the mRNA vaccines based upon similar estimates of vaccine efficacy from adequately designed and well-controlled clinical efficacy endpoint studies; the restoration of immune responses induced by updated vaccine administration and closer matching of immune responses to currently circulating variants. The effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) and subsequent anticipated vaccine strain updates will be evaluated in the Real-World Evidence study conducted as a Post marketing Commitment (PMC).

The known benefit among vaccine recipients 18 years of age and older relative to placebo is reduction in the risk of mild to severe COVID-19 occurring at least 7 days after the second primary series vaccination. Vaccine efficacy estimates from Study 301 are generally consistent across subgroups stratified by demographic variables (including age, race, and ethnicity) and risk for severe COVID-19, with variability in efficacy estimates for some subgroups likely due to small numbers of cases reported in those subgroups. Four severe cases occurred at least 7 days after the second primary series vaccination and all 4 severe cases were in the placebo group. The Original Monovalent vaccine administered as a 2-dose primary series was demonstrated to be efficacious against COVID-19 in an ongoing Phase 3 clinical trial (that supported Emergency Use Authorization). The clinical benefit of a booster dose administered at least 6 months after completion of the primary series is likely related to the restoration of more durable vaccine effectiveness by restoring neutralizing antibody levels in individuals for whom protective immunity has waned. The relevant clinical benefit is related specifically to protection against serious outcomes of COVID-19.

With regard to evidence to support the effectiveness of an Original Monovalent booster dose against the reference SARS-CoV-2 strain and currently circulating SARS-CoV-2 variants, the successful booster dose immunobridging analysis from Study 301, based on neutralizing antibody GMTs against the reference strain (recombinant USA_WA1/2020), supported inference of the booster dose effectiveness in individuals 18 years of age and older who completed a primary series of Original Monovalent. However, the difference in percentages of participants with booster seroconversion and primary seroconversion did not meet the immuno-bridging success criterion. The SCR from pre-booster dose to 28 days post-booster dose (85.4%) was lower than the SCR after the primary series (from baseline pre-Dose 1 to 1 month post-Dose 2) (94.6%), reflecting that a ≥4-fold increase in titer is more difficult to achieve from a booster dose administered to a previously vaccinated individual than from a primary series administered to an individual who is naïve to both SARS-CoV-2 infection and COVID-19 vaccination. An additional descriptive post hoc analysis evaluated SCRs using baseline neutralizing antibody titers prior to Dose 1 of the primary series. The booster dose SCR, with seroconversion defined as at least a 4-fold rise relative to the time of first dose, was 98.3%, with a difference in SCRs in of 3.8% (95% CI: 2.0, 7.0).

Effectiveness of an Original Monovalent heterologous booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 vaccine is inferred from immunogenicity data reported from an independent study conducted in the United

Kingdom (COV-BOOST study), where a booster response to Original Monovalent was demonstrated among individuals who received BNT162b2 for their primary series.

11.2.2 Uncertainties in Benefits

Effectiveness of an Updated Vaccine Formula More Closely Matched to Circulating SARS-CoV-2 Variants of Concern

The effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) administered as a single-dose regimen in individuals 12 years of age and older previously vaccinated with a COVID-19 vaccine can be inferred from the available immunogenicity data. The effectiveness, inferred from immunogenicity, and safety of the modified vaccine (i.e., Omicron BA.1 and Omicron BA.5) and clinical efficacy of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), are relevant to the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) because all these vaccines are manufactured using a similar process, and all used the same antigen and adjuvant dose. It was reasonable to expect from the totality of the available evidence that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) would likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the then circulating predominant Omicron sub lineages, compared with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). However, data are lacking to directly demonstrate vaccine effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) or (2024-2025 Formula) vaccines against COVID-19 outcomes from SARS-CoV-2 Omicron sub lineage infections. Furthermore, other variants, lineages, and sub lineages could emerge against which the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may be less effective.

Duration of Protection

Based on the 28-day post-Dose 3 immunogenicity data submitted for review, there are insufficient immunogenicity data to assess potential sustained effectiveness inferred from persistent antibody levels. There are no validated immune correlates of protection for COVID-19 vaccines and evidence for duration of protection will rely on post-authorization effectiveness studies using Real-World Evidence.

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

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

Effectiveness in Individuals Previously Infected with SARS-CoV-2

There were no COVID-19 cases reported in individuals with prior SARS-CoV-2 infection. However, observational data with other COVID-19 vaccines have demonstrated an added benefit of vaccination to protection conferred solely by naturally acquired immunity (CDC, 2022).

Effectiveness in Pediatric Populations

Data to inform vaccine effectiveness in pediatric age groups (11 years of age and younger) were not included or considered as part of this BLA. Data from studies in pediatric age groups could be considered in BLA supplements to expand the use to include those age groups.

Future Vaccine Effectiveness as Influenced by Characteristics of the Pandemic

The ongoing and uncertain evolution of the disease and its effect on the population, such as increased or decreased infection incidence, emergence of new variants of concern, and/or the effect of coinfections, potentially limit the generalizability and longer-term applicability of the totality of the available evidence to infer effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). Additionally, a large percentage of the population is now seropositive from prior SARS-CoV-2 infections and/or prior COVID-19 vaccination and the effectiveness of future immunizations with updated formulas to reflect virus evolution is likely to be impacted by hybrid immunity with relatively lower effectiveness attributable to vaccination compared with the time when the population was largely SARS-CoV-2-naive. Ongoing evaluation of vaccine effectiveness following licensure is critical to address these uncertainties.

Effectiveness Against Long-Term Effects of COVID-19

Prevention of cases of COVID-19 may result in prevention of some COVID-19 cases with long-term sequelae. Although available data suggests that COVID-19 vaccines currently in use may be beneficial against long-term sequelae of COVID-19, the data are not definitive and additional evaluation post-licensure could be informative.

Effectiveness Against Asymptomatic Infection and Transmission

Available data for the mRNA-based COVID-19 vaccines currently in use has demonstrated that effectiveness against asymptomatic infection is lower and less durable than effectiveness against COVID-19. Available data also do not indicate high-level or durable effectiveness against transmission of SARS-CoV-2 from vaccinated individuals with breakthrough infections. Data for these outcomes are not currently available for the Novavax COVID-19 Vaccines, Adjuvanted; however, it is possible that the observations with other COVID-19 vaccines (with similar antigens and routes of administration) may apply to Novavax COVID-19 Vaccine, Adjuvanted as well.

Effectiveness of booster dose against viral shedding and transmission

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

11.2.3 Known and Potential Risks

Additional doses may be associated with transient local and systemic symptoms like those seen with primary series and prior booster doses.

Important risks that are recognized with Novavax COVID-19 Vaccine, Adjuvanted include myocarditis and/or pericarditis (important identified risk) and ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI) and atrial fibrillation and CVAs (important potential risk)

Myocarditis/pericarditis are known uncommon serious risks associated with the 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) in previously unvaccinated individuals 12 years of age and older. One case of myocarditis in a previously vaccinated 28-year-old male participant was reported 3 days after a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent). Available data from mRNA COVID-19 vaccines suggest that myocarditis/pericarditis risk is greatest in males younger than 40 years of age.

11.2.4 Uncertainties in Risks

Safety in Certain Subpopulations

No clinical safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) are available at this time for certain subpopulations, such as pediatric populations less than 11 years of age, pregnant or lactating women, or in individuals with certain kinds of immunocompromise. For pregnant or lactating women, available safety data from use of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) in nonpregnant, non-lactating women do not raise specific safety concerns for the safety of future use in pregnant or lactating women. However, as noted above, according to CDC as of May 2023 fewer than 90 thousand doses of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) had been administered (outside of clinical studies) in the U.S.

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

It is unknown if the risk of myocarditis/pericarditis would be similar, increased, or decreased following a 2-dose series or a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) as compared with Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) in individuals 12 years of age and older. The risk of ocular motor cranial nerve disorders (i.e., affecting cranial nerves III, IV, or VI) following a 2-dose series or a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is also unknown. In addition, the uncertainty around the risk of hepatic events and myocarditis/pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) as described above, the duration of safety follow-up, and the size of the available booster dose safety database limit the ability to detect the emergence of rare adverse reactions, which may only be identified with broader use and more prolonged safety follow-up. Active and passive safety surveillance will continue postmarketing to detect any new safety signals.

11.3 Discussion of Regulatory Options

The data submitted with this BLA indicate the safety and efficacy of a single dose of Nuvaxovid (2024-2025 Formula) meet the statutory requirements to support its use in individuals 12 years of age and older to prevent COVID-19 caused by SARS-CoV-2. The totality of clinical data provide evidence to support the safety and effectiveness of Nuvaxovid with updates to the strain composition.

11.4 Recommendations on Regulatory Actions

For the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, the clinical reviewers recommend approval of Nuvaxovid (2024-2025 Formula) when administered as a single dose, and that this independent assessment of submitted clinical trial data serve as the basis to support the safety and effectiveness of future periodic strain updates to Nuvaxovid.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved. Based on numeric imbalances seen for atrial fibrillation that were concerning for a potential safety signal, the clinical review team recommended that the following be added to Section 6.1 of the USPI:

> *In the pre-crossover period of Study 1, atrial fibrillation was reported in 13 (0.07%) participants who received Novavax COVID-19 Vaccine, Adjuvanted (Original*

monovalent), and 4 (0.04%) participants who received placebo (of which 10 (0.05%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) arm and 2 (0.02%) participants in the placebo arm experienced events that were serious). Of the total cases reported in the pre-crossover period, onset of atrial fibrillation within 30 days postvaccination occurred in 6 (0.03%) participants compared with 2 (0.02%) participants in the placebo group (of which 3 (0.02%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) arm and 0 participants in the placebo arm experienced events that were serious). The currently available information on atrial fibrillation is insufficient to determine a causal relationship to the vaccine.

In addition, the review team recommended that all previous numeric imbalances that were considered safety signals remain in the USPI. The most clinically relevant of these conditions were cardiomyopathy/ cardiac failure and non-cardiac, non-neurovascular thrombotic and embolic events.

The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

Postmarketing safety monitoring of Nuvaxovid will include routine pharmacovigilance with adverse event reporting under 21 CFR 600.80. The following postmarketing requirement studies will be required under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis following administration of the vaccine:

1. Study 2019nCoV-402, entitled “Safety of the Novavax COVID-19 vaccine in England using a self-controlled case series design: A post-authorisation safety study using data from the Clinical Practice Research Datalink (CPRD) Aurum and linked databases” to evaluate the occurrence of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: March 30, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: June 30, 2028

2. Study 2019nCoV-404, entitled "Safety Profile of the Novavax COVID-19 Vaccine, Adjuvanted in Individuals ≥12 Years of Age in the United States" to evaluate the occurrence of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: June 29, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: September 30, 2028

3. Study 2019nCoV-418, entitled “Post-Authorization Safety Study to Evaluate Long-Term Sequalae of Myocarditis and Pericarditis Following Vaccination” to evaluate long-term sequelae of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID with at least 5 years of follow-up.

   Final Protocol Submission: January 31, 2026

Study Completion Date: December 31, 2031
Final Report Submission: September 31, 2032

The Applicant has made the following postmarketing commitments subject to reporting requirements under Section 506B:

4. Study 2019nCoV-405, entitled “Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)”

   Final Protocol Submission: March 30, 2022 (Submitted)
   Study Completion: February 28, 2027
   Final Report Submission: June 30, 2027

5. Study 2019nCoV-402, entitled “Safety of the Novavax COVID-19 vaccine in England using a self-controlled case series design: A post-authorisation safety study using data from the Clinical Practice Research Datalink (CPRD) Aurum and linked databases” to evaluate the occurrence of atrial fibrillation and cerebrovascular accident following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: March 30, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: June 30, 2028

6. Study 2019nCoV-404, entitled "Safety Profile of the Novavax COVID-19 Vaccine, Adjuvanted in Individuals ≥12 Years of Age in the United States" to evaluate the occurrence of atrial fibrillation and cerebrovascular accident following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: June 29, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: September 30, 2028

As summarized in Section 9.1.3, the Applicant is required to conduct following licensure the PREA deferred studies listed below:

1. Deferred pediatric study under PREA (Study 2019nCoV-503) to evaluate the safety and immunogenicity of Nuvaxovid in COVID-19 vaccine-naïve individuals 6 months to <12 years of age.

   Final protocol submission: March 28, 2022 (Submitted)
   Study completion: October 28, 2025
   Final report submission: March 4, 2026

2. Deferred pediatric study under PREA (Study 2019nCoV-317) to evaluate the immunogenicity of Nuvaxovid in COVID-19 vaccine-naïve seropositive individuals 2 years to <12 years of age and to evaluate the safety and immunogenicity of Nuvaxovid in individuals 6 months to <2 years of age, using a contemporaneously vaccinated comparator group.

   Final protocol submission: April 30, 2025
   Study completion: December 31, 2027
   Final report submission: July 31, 2028

3. Deferred pediatric study under PREA (Study 2019nCoV-506) to evaluate the safety and immunogenicity of Nuvaxovid in COVID-19 vaccine-naïve individuals 0 to <6 months of age.

   Final protocol submission: October 30, 2028
   Study completion: March 31, 2031
   Final report submission: October 31, 2031

During the course of the review, the Novavax agreed to add atrial fibrillation/ atrial flutter and cranial nerve VIII disorders (including vestibular neuronitis) to Studies 402 and 404 as Postmarketing Commitments. The following events were already being evaluated as outcomes in these two studies: myocarditis and/or pericarditis, cerebrovascular accident, ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI), cardiac failure, and cardiomyopathy. The following outcomes will have enhanced pharamacovigilance: atrial fibrillation/ atrial flutter, cranial nerve VIII disorders (including vestibular neuronitis), myocarditis and/or pericarditis, cerebrovascular accident, ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI), cardiac failure, and cardiomyopathy.

Reviewer Comment: The adjustments to the postmarketing surveillance should adequately address all the clinically relevant potential safety signals that were identified during this review and during the EUA review including cardiac failure, cardiomyopathy, atrial fibrillation/ flutter, cerebrovascular accident, and specific cranial nerve disorders.

12. APPENDIX 1. DEATHS

The following tables list the deaths in each vaccination period of the ISS.

Table 110. Deaths in the Pre-Crossover Primary Series (Original Monovalent[a]) Vaccination Period

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-501	ZA001	26	M	5 µg/ 50 µg	2 doses	Completed suicide/ Completed suicide	None	None	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA003	51	F	5 µg/ 50 µg	2 doses	Cervical carcinoma/ Cervical carcinoma	Nur-Isterate and on depo contraception	Hypertension, lower abdominal pain, and vaginal discharge	Section 14.3.2.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA018	63	M	5 µg/ 50 µg	2 doses	COVID-19/ COVID-19	Metformin, lansoprazole, spironolactone, prednisone, diclofenac, paracetamol, calcium, Ridaq, Purgoxin, Lasix, propranolol	Hypertension, diabetes type II, gastric ulcers, edema (pedal), congestive cardiac failure, arthritis, chronic alcoholic liver disease with portal hypertension, obstructive jaundice	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA020	27	M	5 µg/ 50 µg	2 doses	Gun shot wound/ Gun shot wound	None	Anxiety disorder	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA028	68	F	5 µg/ 50 µg	2 doses	COVID-19/ COVID-19	Austell enalapril, Painauio, Vick's Medinite	High blood pressure, arthritis	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA028	67	M	5 µg/ 50 µg	2 doses	Death/ Natural causes	Enalapril, hydrochlorothiazide	Hypertension	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA028	67	F	5 µg/ 50 µg	2 doses	Death/ Natural causes	Hydrochlorothiazide	Hypertension	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA028	80	F	5 µg/ 50 µg	2 doses	Death/ Natural causes	Pharmapress, Adco-Dapamax, hydro-chlorothiazide, loperamide	Hypertension, heart failure BMI=32.2 kg/m^2	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-302	UK010	53	M	5 µg/ 50 µg	1 dose	COVID-19 pneumonia/ COVID-19 pneumonia; broncho-pneumonia	Omeprazole, perindopril, atorvastatin, lercanidipine, indapamide, co-codamol	Hypertension BMI=31.9 kg/m^2	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-302	UK013	66	F	5 µg/ 50 µg	1 dose	Poisoning deliberate/ Morphine and fentanyl toxicity	Citalopram, diazepam, mirtazapine, pregabalin, lansoprazole, sodium docusate, loratadine, estradiol pessary, estradiol patch, paracetamol	Asthma, depression, gastric by-pass, bilateral total knee replacement, atrophic vaginitis, diverticular disease, osteoarthritis, BMI=35.4 kg/m^2	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-302	UK014	65	F	5 µg/ 50 µg	2 doses	Metastasis to liver/ Metastasis to liver	Vitamin Supplement Prime Fifty Strong Bones	Osteoarthritis knees, fibroids, hysteroscopy, and osteoarthritis fingers BMI=23.8 kg/m^2	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-302	UK024	65	M	5 µg/ 50 µg	2 doses	Suicide/ Hanging	None	Migraine	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-302	UK030	76	M	5 µg/ 50 µg	2 doses	Colorectal Adenoma/ Colorectal Adenoma	Allopurinol, amlodipine, amoxicillin, atorvastatin, cyclizine, enoxaparin, gentamicin, meropenem, tazobactam, tamsulosin, tramadol	Benign renal neoplasm, bladder outlet obstruction, blood cholesterol increased, gout, hypertension, nephrectomy	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-301 (Adult Main Study)	US101	60	M	5 µg/ 50 µg	2 doses	Toxicity to various agents/ Cardiac arrest	Metformin, atorvastatin, tamsulosin, acetylsalicylic acid, beta-blocker, and statin	Prostate hypertrophy, non-obstructive coronary artery disease, patent left main, cocaine abuse, moderate disease of the left anterior descending artery and right coronary artery, hypercholesterolemia, prediabetes	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US162	40	F	5 µg/ 50 µg	2 doses	Accidental overdose/ Alcohol, cocaine, and fentanyl intoxication	Effexor, Wellbutrin, Adderall, Haldol, Remeron, Klonopin, naproxen, omeprazole, Lyrica, influenza vaccine, Trintellix	Attention deficit disorder, anxiety, depression, insomnia, osteoarthritis, back pain, fibromyalgia, tachycardia, gastric bypass sleeve, spinal decompression	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US172	74	F	5 µg/ 50 µg	2 doses	Cerebrovascular accident/ Cerebrovascular accident	Atenolol, levothyroxine, bupropion, pramipexole, Prolia	Hypertension, hypothyroidism, anxiety disorder; osteoporosis, restless leg syndrome. Fatal following thrombectomy and hemorrhagic conversion of MCA and ICA.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US178	66	M	5 µg/ 50 µg	1 dose	Cardiac arrest/ Cardiac arrest	None	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US206	39	M	5 µg/ 50 µg	2 doses	Cardiac arrest/ Cardiac arrest	Humalog, Lantus, lisinopril, Abilify, mirtazapine, and albuterol	Asthma, hypertension, Type 1 diabetes mellitus, hypertension, illicit drug use, drug screen positive for THC and cocaine.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US206	26	F	5 µg/ 50 µg	2 doses	Gunshot wound/ Gunshot wound	None	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US216	50	M	5 µg/ 50 µg	2 doses	Cardiac arrest/ Cardiac arrest	Aspirin, lisinopril, Novolog, Levemir, ibuprofen, simvastatin	Insulin-dependent type 2 diabetes mellitus, hypertension, bilateral diabetic foot ulcers, chronic alcohol abuse, peripheral diabetic neuropathy bilateral feet.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US216	45	M	5 µg/ 50 µg	2 doses	Cardiac arrest/ Cardiac arrest	Lisinopril, albuterol, acetaminophen, pantoprazole, Paxil, sertraline, propranolol	Asthma, hypertension, type 2 diabetes mellitus, hemorrhage of GI tract, alcohol abuse, iron deficiency anemia, chronic alcohol dependence, recurrent major depression, and methamphetamine disorder; BMI=33.9 kg/m^2.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US223	63	M	5 µg/ 50 µg	2 doses	Septic shock/ Septic shock	None	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US226	44	F	5 µg/ 50 µg	1 dose	Cardiac arrest/ Cardiac arrest	Albuterol-ipratropium, buspirone, lisinopril, risperidone, albuterol	Amphetamine abuse, asthma, nicotine dependence, hypertension, and hysterectomy; BMI=40.7 kg/m^2	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Source: ISS Table 117, pages 261-287

Abbreviations: ADD=attention-deficit disorder; BMI=body mass index; COPD=chronic obstructive pulmonary disorder; COVID-19=coronavirus disease 2019; CTA=computed tomographic angiography; DM=diabetes mellitus; EUA=Emergency Use Authorization; F=female; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HIV=human immunodeficiency virus; HTCZ=hydrochlorothiazide; ICA=internal carotid artery; M=male; MCA=middle cerebral artery; MVA=motor vehicle accident; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; THC=tetrahydrocannabinol; TIA=transient ischemic attack; UK=United Kingdom; U.S.=United States; ZA=South Africa.

a. Five participants were censored from the ISS in the Pre-Crossover Primary Series Vaccination Period, with 3 participants in the Adult Main Study of Clinical Study 2019nCoV-301 and 2 participants in Clinical Study 2019nCoV-302 as follows: Clinical Study 2019nCoV-301: A U.S. participant (Original Monovalent) who died due to myocardial infarction, was censored from the ISS for unblinding prior to the date of death; a U.S. participant (placebo) who died due to an SAE an unknown cause of death, was censored from the ISS for receiving doses of Pfizer COVID-19 vaccine prior to his death; and a U.S. participant (placebo) who died due to a cardiac arrest, was censored for receiving an unspecified COVID-19 vaccine from another facility prior to his death; Clinical Study 2019nCoV-302: a UK participant (placebo) who died due to glioblastoma, and a UK participant (Original Monovalent) who died due to COVID-19 pneumonia, were censored from the ISS because the deaths occurred after the ISS-defined end of follow-up date for the Pre-Crossover Primary Series Vaccination Period.

b. Dose of SARS-CoV-2 rS (antigen)/dose of Matrix-M adjuvant (adjuvant).

Table 111. Deaths in the Placebo to Original Monovalent Vaccination Period

Study	Center	Age (y)	Sex	Dose[a] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-501	ZA014	58	M	5 µg/ 50 µg	2 doses	Respiratory tract infection/ Natural causes	None	Tuberculosis and chest infections	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA018	31	M	5 µg/ 50 µg	2 doses	Death/ Potentially related to murder	None	None	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA019	27	M	5 µg/ 50 µg	1 dose	Gun shot wound/ Gun shot wound	None	None	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA020	44	F	5 µg/ 50 µg	2 doses	Type 2 diabetes mellitus/ Natural causes	Tenofovir, emtricitabine, efavirenz, Actraphane	Type 2 diabetes mellitus, asthma, hypertension, acne vulgaris, and abnormal uterine bleeding, HIV positive	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-501	ZA021	25	M	5 µg/ 50 µg	2 doses	Physical assault/ Unnatural causes (deep head injury)	None	None	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report

Study	Center	Age (y)	Sex	Dose[a] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-501	ZA028	71	F	5 µg/ 50 µg	2 doses	Cerebrovascular accident Lower respiratory tract infection Death/ Natural causes	Amlodipine and Asthmavent	Hypertension, asthma, atrial fibrillation (chronic condition), and stroke	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report
2019nCoV-302	UK030	52	M	5 µg/ 50 µg	2 doses	Myocardial ischemia, cardiac arrest/ Myocardial ischemia, cardiac arrest	Perindopril, Indapamide MR, amlodipine, Loratadine, fluoxetine, Colofac, paracetamol	Hypertension, fatty liver disease, alcohol use (50 units/week), former smoker, depression, BMI=34.2 kg/m^2	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-301 (Adult Main Study)	US171	62	M	5 µg/ 50 µg	2 doses	Death/ Unknown	Metformin, atorvastatin, sildenafil, Voltaren	MVA victim, pronounced dead at scene, was a passenger	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US171	57	F	5 µg/ 50 µg	2 doses	Road traffic accident/ Road traffic accident	Clopidogrel, glimepiride, atorvastatin, lisinopril, triamterene-hydrochlorothiazide, Janumet XR, ASA, Basaglar, Bupropion, Buspar	MVA victim, pronounced dead at scene, was the driver. History of anxiety/panic attack; TIA, stroke, osteoarthritis, high blood pressure, DM type II/ obesity	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US149	82	M	5 µg/ 50 µg	2 doses	Atherosclerotic cardiovascular disease/ Arteriosclerosis	Amlodipine, atorvastatin calcium, glibenclamide, metformin hydrochloride, insulin glargine, pioglitazone	Alopecia, Cataract, Clavicle fracture, Dermal cyst, Dermatitis, Dyslipidemia, Gastroesophageal reflux disease, Hemorrhoid operation, Hypertension, Intestinal polyp, Myopia, Obesity, Polyarthritis, Presbyopia, Prostate cancer, Rotator cuff repair, Tonsillectomy, Type 2 diabetes mellitus, Vertigo	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US177	67	M	5 µg/ 50 µg	2 doses	Septic shock/ Septic shock	Morphine, zolpidem, Tivicay, Descovy, mirtazapine, pravastatin, pantoprazole, lisinopril, venlafaxine, Combivent Respimat, doxepin	COPD, HIV, CTA chest showed adjacent soft tissue paraspinal mass 5 days prior to death, diagnosed with esophageal cancer 4 days prior to death	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[a] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US179	63	F	5 µg/ 50 µg	2 doses	Angiosarcoma/ Angiosarcoma	Alendronate sodium, botulinum toxin type A, bupropion hydrochloride, cannabis sativa, cefalexin, cefepime, celecoxib, clindamycin, cholecalciferol, dexamethasone, doxycycline, erenumab-aooe, fentanyl, gabapentin, hydrocodone, paracetamol, hydromorphone	Allergy to chemicals, anxiety, asthma, back pain, breast cancer, breast conserving surgery, cataract, cataract operation, cholecystectomy, cholelithiasis, depression, dermatitis contact, drug hypersensitivity, fibromyalgia, gastric bypass, gastroesophageal reflux disease, insomnia, intervertebral disc protrusion, irritable bowel syndrome, knee arthroplasty, migraine, osteoarthritis, osteoporosis, overweight, post menopause, sciatica, sleep apnea syndrome, spinal compression fracture, squamous cell carcinoma of skin.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US187	18	F	5 µg/ 50 µg	2 doses	Accidental Overdose/ Accidental Overdose	Guanfacine	Anxiety, asthma, back pain, bulimia nervosa, disruptive mood dysregulation disorder, nicotine dependence, obesity, post-traumatic stress disorder, substance use	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US216	23	F	5 µg/ 50 µg	2 doses	Multiorgan Failure/ Multiorgan Failure	Calcium Chloride, potassium chloride, sodium lactate, ceftriaxone, contraceptives for topical use, etonogestrel, fluoxetine hydrochloride, ibuprofen, lactic acid, metronidazole, norepinephrine, paracetamol, phenylephrine, piperacillin sodium, tazobactam, sodium, red blood cells concentrated, sodium chloride	Alcohol abuse, major depression, overweight, pain, substance abuse, tobacco abuse, transdermal contraception	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[a] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US216	35	F	5 µg/ 50 µg	2 doses	Aneurysm ruptured/ Cerebral anoxia, consequence of aneurysm ruptured	loratadine, lisinopril	History of alcohol use; had been taken into police custody for an unknown reason at the time of the events; history of upper GI bleed and seizure; hypertension atrial fibrillation; tobacco use	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US232	46	M	5 µg/ 50 µg	2 doses	Cardiac arrest/ Cardiac arrest	Adderall, Seroquel	Obesity, ADD	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US237	36	M	5 µg/ 50 µg	2 doses	Toxicity to various agents/ Toxic effects of fentanyl	Topiramate, trazadone, fluoxetine	Alcohol abuse with tolerance and dependence and opioid abuse both since 2004, polysubstance abuse, history of recurrent psychiatric hospitalizations for detoxification since the age of 20 including one that happened while on study, reported to consume one-fifth to one-half of vodka and or one case of beer daily	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Source: ISS Table 117, pages 261-287
Abbreviations: ADD=attention-deficit disorder; BMI=body mass index; COPD=chronic obstructive pulmonary disorder; COVID-19=coronavirus disease 2019; CTA=computed tomographic angiography; DM=diabetes mellitus; EUA=Emergency Use Authorization; F=female; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HIV=human immunodeficiency virus; HTCZ=hydrochlorothiazide; ICA=internal carotid artery; M=male; MCA=middle cerebral artery; MVA=motor vehicle accident; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; THC=tetrahydrocannabinol; TIA=transient ischemic attack; UK=United Kingdom; U.S.=United States; ZA=South Africa.
a. Dose of SARS-CoV-2 rS (antigen)/dose of Matrix-M adjuvant (adjuvant).
b. Participant was not included in the Post-Crossover Primary Series Vaccination Period, since Clinical Study 2019nCoV-501 was excluded from the analysis set for this vaccination period, rather the participant was included in the Combined Pre- and Post-Crossover Primary Series Vaccination Period.

Table 112. Deaths in the Original Monovalent to Placebo[a] Vaccination Period

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-302	UK005	48	F	5 µg/ 50 µg	2 doses	Completed suicide/ Asphyxiation due to hanging	None	Nasoplasty, blocked nose, Caesarean section, and tubal sterilization	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-302	UK007	51	M	5 µg/ 50 µg	2 doses	Sudden death/ Sudden death	Odefsey, sertraline	HIV, depression	Section 14.3.2.1 of 2019nCoV-302 Clinical Study Report Safety Narrative Addendum
2019nCoV-301 (Adult Main Study)	MX009	96	M	5 µg/ 50 µg	2 doses	Acute myocardial infarction secondary to diabetes mellitus/ Sudden cardiac death	Candesartan, dutasteride, elasomeran, levofloxacin, levothyroxine, metformin, nitrofurantoin, rosuvastatin, sitagliptin, tamsulosin	Benign prostatic hyperplasia, hypercholesterolemia, hypertension, type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US049	57	M	5 µg/ 50 µg	2 doses	Cardiac arrest/ Myocardial Infarction	Amiodarone, epinephrine, hydrochlorothiazide, lisinopril, metformin	Hypertension, overweight, type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US053	79	M	5 µg/ 50 µg	2 doses	Ischemic stroke/ Aspiration pneumonia, dysphagia	Fluticasone propionate/salmeterol, ipratropium bromide/albuterol sulfate, albuterol, tizanidine, hydrocodone	Age, COPD, preceding head trauma	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US073	41	M	5 µg/ 50µg	2 doses	Road traffic accident/ Road traffic accident	None	Seasonal Allergy	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US074	44	M	5 µg/ 50 µg	2 doses	Death/ Unknown	None	Recent gastrointestinal illness, BMI=43.7 kg/m^2.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US081	53	F	5 µg/ 50 µg	2 doses	Chronic obstructive pulmonary disease/ Chronic obstructive pulmonary disease	Atorvastatin, cetrizine hydrochloride, fluticasone furoate, umeclidinium bromide, vilanterol trifenantate, gabapentin, loratidine, naproxen, omeprazole, prednisone, salbutamol, ziprasidone	Allergy to chemicals, anxiety, asthma, bipolar disorder cervical dysplasia, depression, drug hypersensitivity, dyslipidemia, emphysema, gastro esophageal reflux disease, obesity, oedema peripheral, seasonal allergy, tension headache	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US104	65	F	5 µg/ 50 µg	2 doses	Death/ Unknown	Trazodone	Hysterectomy, insomnia, therapeutic procedure	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US142	61	M	5 µg/ 50 µg	2 doses	Myocardial infarction/ Myocardial infarction	Prilosec	Tobacco use since 1962	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US147	84	M	5 µg/ 50 µg	2 doses	Death/ Unknown	Acetyl salicyclic acid, amlodipine, apixaban, atorvastatin, levothyroxine sodium, pembrolizumab	Dyslipidemia, hypertension, hypothyroidism, inguinal hernia	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US152	64	F	5 µg/ 50 µg	2 doses	Chronic obstructive pulmonary disease/ Chronic obstructive pulmonary disease	Alprazolam, docusate sodium, influenza vaccine, lamotrigine, metformin, omeprazole, pneumococcal vaccine, propanalol, topiramate, venlafaxine,	Bipolar disorder, Caesarean section, Constipation, Depression, Dyspepsia, Female sterilisation, Haemorrhoids, Hypertension, Iron deficiency, Obesity, Post herpetic neuralgia, Postmenopause, Sciatica, Sleep apnoea syndrome, Type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US159	41	M	5 µg/ 50 µg	2 doses	Death/ Death	Atorvastatin, dapagliflozin, glimepiride, insulin glargine, insulin lispro, lisinopril	Hypercholesterolaemia, Hypertension, Obesity, Pain in extremity, Seasonal allergy, Skin exfoliation, Type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US164	27	M	5 µg/ 50 µg	2 doses	Completed suicide/ Exsanguination secondary to contact gunshot wound to the chest	Gabapentin, Albuterol, Symbicort, Lexapro	Anxiety, depression	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US170	53	F	5 µg/ 50 µg	2 doses	Respiratory failure and chronic obstructive pulmonary disease/ Respiratory failure with chronic obstructive pulmonary disease as underlying cause	Lamictal, Trintellix, Lyrica, trazadone, Zanaflex, diazepam, and oxycodone	Tobacco use, BMI=33.9 kg/m^2, bipolar disorder, depression, insomnia, and anxiety	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US178	68	M	5 µg/ 50 µg	2 doses	Cardiac arrest and chronic obstructive pulmonary disease/ Cardiac arrest and chronic obstructive pulmonary disease	None	Hypertension	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US179	73	M	5 µg/ 50 µg	2 doses	Multiple organ dysfunction syndrome/ Cardiac arrest	Allopurinol, Azithromycin, Budesonide-Formoterol, Ceftriaxone sodium, Clotrimazole, Doxycycline, Fluconazole, Hydrochlorothiazide-Olmesartan, Ipratropium Bromide, Montelukast, Olmesartan	Asthma, Bacterial disease carrier, Basal cell carcinoma, Deafness, Dermatitis contact, Erectile dysfunction, Fungal infection, Gout, Hypermetropia, Hypertension, Inguinal hernia, Inguinal hernia repair, Knee arthroplasty, Muscle spasms, Overweight, Seasonal allergy, Skeletal injury. Squamous cell carcinoma of skin, Tremor, Waldenstrom's macroglobulinaemia	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US179	64	F	5 µg/ 50 µg	2 doses	Chronic obstructive pulmonary disease/ End-stage chronic obstructive pulmonary disease exacerbation	Montelukast, Advair, Albuterol, and Pulmicort	History of chronic obstructive pulmonary disease, BMI=31.1 kg/m^2	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US191	48	M	5 µg/ 50 µg	2 doses	Toxicity to various agents/ Acute alprazolam, oxycodone, oxymorphone intoxication	Zyrtec, pseudoephedrine hydrochloride	Seasonal allergies, penicillin allergy, and atrial fibrillation	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US194	58	M	5 µg/ 50 µg	2 doses	Cardiomyopathy alcoholic/ Alcoholic cardiomyopathy	Albumin human, bumetanide, carvedilol, Sublimaze, Reglan, Zofran, Vancocin	History of acute renal failure with dialysis, tobacco use, alcohol use, and concurrent end stage liver disease	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US204	79	M	5 µg/ 50 µg	2 dose	Cardiac failure congestive/ Cardiac failure congestive	Bupropion, Carvedilol, Furosemide, Metformin, Omeprazole, Salbutamol sulfate, Tamsulosin, Trazodone, Venlafaxine	Asthma, Basal cell carcinoma, Benign prostatic hyperplasia, Cardiac failure congestive, Cardiac pacemaker insertion, Cardiac pacemaker replacement, Cataract operation, Coronary artery bypass, Depression, Eczema, Gastrooesophageal reflux disease, Hip fracture, Hypoaesthesia, Infusion, Insomnia, Iron deficiency anaemia, Joint surgery, Malignant melanoma, Mycotic allergy, Renal cyst, Rheumatoid arthritis, Seasonal allergy, Tonsillectomy, Tonsillitis, Type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US208	64	F	5 µg/ 50 µg	2 doses	Death/ Natural Cause and other contributing conditions included hypertension and mitral valve regurgitation	Atenolol, Calcium carbonate, Colecalciferol	Acute pulmonary oedema, Arrhythmia, Arthritis reactive, Breast cancer, Hypertension, Mitral valve incompetence, Radiotherapy, Sleep apnoea syndrome	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US216	51	F	5 µg/ 50 µg	2 doses	Septic shock/ Septic shock	Albumin human, Blood Plasma, Ceftriaxone, Ceftriaxone sodium, Midodrine, Octreotide, Pantoprazole sodium sesquihydrate, Piperacillin sodium-Tazobactam, Bed blood cells concentrated, Rifaximin	Alcohol abuse, Cholecystectomy, Essential hypertension, Female sterilization, Insomnia, Ligament operation, Meniscus operation, Menopause, Persistent depressive disorder, Secondary hypertension, Substance abuse, Vitamin D deficiency	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US216	45	F	5 µg/ 50 µg	2 doses	Hepatorenal syndrome/ Multiorgan failure	Advair	Alcoholic liver cirrhosis; alcohol dependence; tobacco use since 1987; chronic hypertension; anemia of chronic disease; general social phobia; depressive disorder; abnormal liver enzymes since 2017; substance abuse	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US216	39	M	5 µg/ 50 µg	2 doses	Emphysematous pyelonephritis/ Septic shock and Bilateral emphysematous pyelonephritis	Albumin human, Amiodarone, Cefepime, Esmolol, Menthol-Methyl Salicylate, Norepinephrine, Bitartrate, Pantoprazole sodium sesquihydrate, Phenylephrine, Piperacillin sodium-Tazobactam sodium, Platelets, Sodium chloride, vancomycin, vasopressin	Arthralgia, Contusion, Fractured coccyx, Overweight, Tobacco abuse, Tonsillectomy, Type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US247	29	M	5 µg/ 50 µg	2 doses	Death/ Unknown	Sertraline, mirtazapine	Depression	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US232	70	M	5 µg/ 50 µg	2 doses	COVID-19 pneumonia/ COVID-19 pneumonia	Glimepiride, hydrochlorothiazide, lisinopril, metformin	Hyperlipidemia, hypertension, myopia, type 2 diabetes mellitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US239	63	M	5 µg/ 50 µg	2 doses	Death/ Unknown	Influenza vaccine, lysine	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US240	51	F	5 µg/ 50 µg	2 doses	Road traffic accident/ Motor vehicle accident	Aripiprazole	Bipolar disorder	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US245	41	M	5 µg/ 50 µg	2 doses	Victim of homicide/ Gunshot wound	None	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US248	72	M	5 µg/ 50 µg	2 doses	Cardiomyopathy/ Cardiomyopathy and coronary artery disease	Acetylsalicylic acid, nictotinic acid, baclofen, bisoprolol, fluocinonide, formoterol fumarate, mometasone furoate, methylprednisolone	Asthma, cardiac failure, cardiomyopathy, cataract, colonoscopy, coronary artery disease, dermatitis, drug hypersensitivity, GERD, heart rate increased, hypertension, prostatomegaly, skin neoplasm excision, tinnitus	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US249	29	M	5 µg/ 50 µg	2 doses	Toxicity to various agents/ Multiple controlled substances	None	None	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Source: ISS Table 117, pages 261-287

Abbreviations: ADD=attention-deficit disorder; BMI=body mass index; COPD=chronic obstructive pulmonary disorder; COVID-19=coronavirus disease 2019; CTA=computed tomographic angiography; DM=diabetes mellitus; EUA=Emergency Use Authorization; F=female; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HIV=human immunodeficiency virus; HTCZ=hydrochlorothiazide; ICA=internal carotid artery; M=male; MCA=middle cerebral artery; MVA=motor vehicle accident; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; THC=tetrahydrocannabinol; TIA=transient ischemic attack; UK=United Kingdom; U.S.=United States; ZA=South Africa.

a. One participant in the Adult Main Study of 2019nCoV-301 was censored from the ISS in the Post-Crossover Primary Series Vaccination Period because their death occurred after the ISS-defined end of follow-up date of the Post-Crossover Primary Series Vaccination Period: a U.S. participant (Original Monovalent to Placebo) died due to unknown cause of death.

b. Dose of SARS-CoV-2 rS (antigen)/dose of Matrix-M adjuvant (adjuvant).

Table 113. Deaths in the Homologous/Heterologous Booster Vaccination Period[a]

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-501	ZA028	55	M	5 µg/ 50 µg	1 dose	Renal failure Death/ Natural causes	Cipalat Retard and captopril	Hypertension, congestive heart failure, and inadequately managed renal impairment	Section 14.3.2.1 of 2019nCoV-501 12-Month Clinical Study Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US081	70	M	5 µg/ 50 µg	1 dose	Arrhythmia/ Cardiac arrhythmia	Amitriptyline hydrochloride, amlodipine, Aspirin, and Lantus	Angina, diabetes type-2, hypertension, chronic renal disease stage 4, gout, dyslipidemia, and neuropathy; BMI of 27.7 kg/m^2	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US144	68	M	5 µg/ 50 µg	1 dose	Sepsis/ Sepsis	Aspirin, lovastatin, furosemide, pantoprazole sodium, spironolactone, losartan potassium, metformin, Jardiance, and Tresiba flextouch	Non-alcoholic hepatosteatosis, Barrett's esophagitis with dysplasia, type II diabetes, obesity, sleep apnea, peripheral vascular disease, asymptomatic proteinuria, non-rheumatic aortic valve stenosis, hyperglycemia, hyperpigmentation of lower extremities, and iron deficiency anemia	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US164	53	M	5 µg/ 50 µg	1 dose	Cardiac arrest/ Cardiac arrest	Amlodipine, Klor-con, omeprazole, furosemide, allopurinol, Banophen, ibuprofen, albuterol sulphate, budesonide, carvedilol, cetirizine, Flonase, Norco, hydroxyzine pamoate, and metformin	Hypertension, sleep apnea, type II diabetes mellitus, chronic obstructive pulmonary disease, and congestive cardiac failure; BMI of 48.9 kg/m^2.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US170	43	F	5 µg/ 50 µg	1 dose	Death/ Unknown	Diphenhydramine hydrochloride, lamotrigine, propranolol, tizandine, topiramate	Brain lobectomy, cholecystectomy, cholelithiasis, drug hypersensitivity epilepsy, female sterilization, headache, hypertension, meningitis, migraine, seasonal allergy, thyroid cyst, thyroid cystectomy, tonsillectomy,	Section Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US179	60	F	5 µg/ 50 µg	1 dose	Cardiac Arrest/ Cardiac Arrest	Acetylsalicylic acid, adrenergic and dopaminergic agents, amitriptyline, amoxicillin, atorvastatin, budesonide, formoterol, fumarate, clopidogrel bisulfate, diphenhydramine hydrochloride, dulaglutide, empagliflozin, enoxaparin sodium, famotidine, furosemide, insulin, lidocaine, losartan, metoprolol, olopatadine hydrochloride, pregabalin, warfarin, triamcinolone acetonide	Angina pectoris, anxiety, asthma, back pain, blood cholesterol increased, blood triglycerides increased, carpal tunnel syndrome, coronary arterial stent insertion, depression, diabetic neuropathy, drug sensitivity, dyspepsia, endometriosis, fibromyalgia, GERD, hypertension, insomnia, hypertonic bladder, mitral valve incompetence, mitral valve repair, myocardial infarction, myopia, oedema peripheral, peripheral arterial occlusive disease, peripheral artery stent insertion, postmenopause, TIA, type 2 diabetes mellitus, uterine leiomyoma	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US194	81	F	5 µg/ 50 µg	1 dose	Septic shock/ Septic shock	Atorvastatin calcium, lisinopril/hydro-chlorothiazide, Eliquis, and metoprolol	Hysterectomy, bladder sling, hypercholesterolemia, hypertension, obesity (BMI=30 kg/m^2), and atrial fibrillation	Section 14.3.11.1 of 019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US201	61	M	5 µg/ 50 µg	1 dose	Esophageal adenocarcinoma stage IV/ Cardiopulmonary arrest due to stage 4 esophageal cancer	Amlodipine and Allegra	Hypertension, LINX procedure, Barrett esophagus, and gastroesophageal reflux disease; BMI=21.4 kg/m^2.	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report
2019nCoV-301 (Adult Main Study)	US204	20	M	5 µg/ 50 µg	1 dose	Road traffic accident/ Road traffic accident	Amitriptyline, loratadine, hydrocortisone, hydroxyzine, and losartan	Asthma, intermittent headaches, seasonal allergies, dry skin, and gastritis; BMI=34.9 kg/m^2	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Study	Center	Age (y)	Sex	Dose[b] (units)	Duration of Exposure	Diagnosis/ Cause of Death	Other Medications	Other Medical Conditions	Location of Narrative Description
2019nCoV-301 (Adult Main Study)	US216	44	M	5 µg/ 50 µg	1 dose	Cardiac arrest/ Cardiac arrest, underlying causes of death were hepatic cirrhosis and alcoholic liver cirrhosis, and high blood pressure	Vitamin D, glipizide, metformin, spironolactone, and Lasix	Nicotine dependence and tobacco use, substance abuse, adjustment disorder with anxious mood, anxiety, type 2 diabetes mellitus, chronic alcohol dependence, and cirrhosis; BMI=24.8 kg/m^2	Section 14.3.11.1 of 2019nCoV-301 17-Month Interim Report

Source: ISS Table 117, pages 261-287

Abbreviations: ADD=attention-deficit disorder; BMI=body mass index; COPD=chronic obstructive pulmonary disorder; COVID-19=coronavirus disease 2019; CTA=computed tomographic angiography; DM=diabetes mellitus; EUA=Emergency Use Authorization; F=female; GERD=gastroesophageal reflux disease; GI=gastrointestinal; HIV=human immunodeficiency virus; HTCZ=hydrochlorothiazide; ICA=internal carotid artery; M=male; MCA=middle cerebral artery; MVA=motor vehicle accident; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; THC=tetrahydrocannabinol; TIA=transient ischemic attack; UK=United Kingdom; U.S.=United States; ZA=South Africa.

a. Five participants were censored from the ISS in the Homologous Booster Vaccination Period because their deaths occurred after the ISS-defined end of follow-up date for the Homologous Booster Vaccination Period, with 4 participants in the Adult Main Study of 2019nCoV-301 and 1 participant in Clinical Study 2019nCoV-501 as follows: Adult Main Study of Clinical Study 2019nCoV-301: a U.S. participant (Original Monovalent booster) who died due to toxicity to various agents (fentanyl and cocaine intoxication); a U.S. participant (Original Monovalent booster) who died due to myocardial infarction; a U.S. participant (Original Monovalent booster) who died due to death (unknown); and a U.S. participant (Original Monovalent booster) who died due to cirrhosis alcoholic; Clinical Study 2019nCoV-501: a participant from South Africa (Original Monovalent booster) who died due to tongue neoplasm, was censored from the ISS as date of death occurred after study discontinuation.

b. Dose of SARS-CoV-2 rS (antigen)/dose of Matrix-M adjuvant (adjuvant).

13. APPENDIX 2. POTENTIAL IMMUNE-MEDIATED MEDICAL CONDITIONS

Table 114. Potential Immune-Mediated Medical Conditions

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

Source: Adapted from 2019nCoV-301 Table 11. IND 22430.
Abbreviations: ANCA=anti-neutrophil cytoplasmic antibody; CREST=calcinosis, Raynaud's phenomenon; esophageal dysmotility; sclerodactyly, telangiectasia; IgA=immunoglobulin A; MedDRA=Medical Dictionary for Regulatory Activities