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

Identifying Information

Application Type	EUA Amendment
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Sponsor	Novavax Inc.,
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Signatory Authority	David C. Kaslow, M.D., Director, OVRR
Principal Reviewers	Paul Keller, Ph.D., Regulatory Project Manager, OVRR/DVRPA CAPT Edward Wolfgang, Ph.D., Regulatory Project Manager, OVRR/DVRPA Goutam Sen, Ph.D., Regulatory Project Manager, OVRR/DVRPA Donna Elhindi, PharmD, Regulatory Project Manager, OVRR/DVRPA Amina White, M.D., Primary Clinical Reviewer, OVRR/DVRPA Charles Line, M.D., Clinical Reviewer, OVRR/DVRPA Ravi Goud, M.D., Clinical Reviewer, OVRR/DVRPA Brenda Baldwin, Ph.D., Data Integrity Reviewer, OVRR/DVRPA Rositsa Dimova, Ph.D., Clinical Biostatistics Reviewer, OBPV/DB Kumaresh Dhara, Ph.D., Clinical Biostatistics Reviewer, OBPV/DB Xinyu Tang, Ph.D., Clinical Biostatistics Reviewer, OBPV/DB Fang Chen, Ph.D. Nonclinical Biostatistics Reviewer, OBPV/DB Afolabi (Clement) Meseda, Ph.D., CMC/Product OVRR/DVP Marina Zaitseva Ph.D., CMC/Adjuvant Reviewer OVRR/DVP Arifa Khan, Ph.D. CMC Adventitious Agent Reviewer Gregory Price, CMC/Facility Reviewer, OCBQ/DMPQ Osman N. Yogurtcu, Ph.D., Benefit-Risk OBPV/DABRA Xinyi Ng, Ph.D., Benefit-Risk OBPV/DABRA Debbie Vause, R.N. DMPQ RPM Brendan Day, M.D., M.P.H., PVP Reviewer, OBPV/DPV CAPT Oluchi Elekwachi, PharmD, MPH, Labeling Reviewer, OCBQ/DCM/APLB Daphne Stewart, Labeling Reviewer, OVRR/DVRPA
Review Completion Date	October 03, 2023
Established Name/Names used during development	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)
Dosage Forms/Strengths and Route of Administration	A 0.5 mL suspension for intramuscular injection (for 12 years of age and older (For dosing regimen, dose, and schedule, refer to Section 5.1)
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2)
Intended Population	Individuals 12 years of age and older

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Glossary

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CT	computerized tomography
DP	drug product
DS	drug substance
ECMO	extracorporeal membrane oxygenation
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HHS	U.S. Department of Health and Human Services
ICSR	Individual Case Safety Report
IND	Investigational New Drug Application
MAAE	medically attended adverse event
MN50	microneutralization assay with an inhibitory concentration of 50%
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
O/E	observed-to-expected
PCR	polymerase chain reaction
PIMMC	potential immune-mediated medical condition
PT	preferred term
qELISA	quantitative enzyme-linked immunosorbent assay
RBD	receptor binding domain
rS	recombinant spike glycoprotein
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCR	seroconversion rate
SRR	seroresponse rate
U.S.	United States of America
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine effectiveness
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 Executive Summary

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an ongoing global health challenge. As of September 21, 2023, SARS-CoV-2 has led to over 770 million cases of coronavirus disease 2019 (COVID-19), approximately 7 million deaths worldwide, and has caused societal, economic, and healthcare system disruptions. COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19. COVID-19 vaccinations have been estimated to have prevented tens of millions of deaths worldwide in the first year alone after COVID-19 vaccines became available in December 2020.[1]

The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is a nanoparticle vaccine that contains full-length recombinant SARS-CoV-2 spike protein based on the ancestral (Wuhan) strain, stabilized in its pre-fusion conformation, and produced from baculovirus infected Sf9 (fall armyworm) insect cells. Hereafter referred to as Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), it also contains Matrix-M adjuvant comprised of saponins derived from the soapbark tree (*Quillaja saponaria* Molina). Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is currently authorized for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older as a 2-dose series of 5 µg recombinant spike protein and 50 µg of Matrix-M adjuvant administered 3 weeks apart, and in certain individuals 18 years of age and older, as a single dose at least 6 months after prior vaccination with an authorized or approved COVID-19 vaccine. On July 13, 2022, FDA first authorized the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for use under emergency use authorization (EUA) as a 2-dose series of 5 µg recombinant spike protein and 50 µg of Matrix-M adjuvant administered 3 weeks apart for individuals 18 years of age and older. On August 19, 2022, the EUA was amended to include use of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) as a 2-dose series in individuals 12 through 17 years of age. On October 19, 2022, FDA amended the EUA to include use of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) as a single dose, six months after the last COVID-19 Vaccine, in individuals 18 years of age and older for whom an FDA-authorized messenger ribonucleic acid (mRNA) bivalent COVID-19 booster vaccine was not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) because they would otherwise not receive a dose of a COVID-19 vaccine. For additional details, please refer to Novavax COVID-19 Vaccine, Adjuvanted | FDA.

Although real-world effectiveness studies suggest that the bivalent COVID-19 vaccines (Original and Omicron BA.4/BA.5), which are no longer authorized for use in the U.S., continue to provide protection against circulating sublineages of Omicron, including XBB.1.5,[2,3] there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that vaccine effectiveness against Omicron sublineages appears to wane over time.[3] Recent epidemiology data indicate that SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations. By mid-September 2023, Omicron XBB-lineage descendants accounted for >95% of the circulating SARS-CoV-2 sublineages in the U.S. (see Section 3). To ensure that COVID-19 vaccines remain effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages, an update to the strain composition of COVID-19 vaccines to match more closely the currently circulating Omicron sublineages is warranted.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has convened in

open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. On June 15, 2023, VRBPAC voted to recommend an update of the current COVID-19 vaccine composition to a monovalent XBB-lineage, with preference for the XBB.1.5 sublineage. FDA subsequently advised manufacturers updating their COVID-19 vaccines to develop vaccines with a monovalent XBB.1.5 composition for the 2023-2024 Formula (refer to Section 3.2).

On September 6, 2023, Novavax requested authorization of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), to include a single-dose for individuals 12 years of age and older previously vaccinated with any COVID-19 vaccine (refer to Section 5), supported by effectiveness and safety data as described below.

Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) Effectiveness

Dosage based on prior vaccination status:
Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted in individuals 18 years of age and older not previously vaccinated with any COVID-19 vaccine was previously demonstrated in a large Phase 3 clinical efficacy trial (see Section 6.2.4 of the Decision Memorandum).

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted in individuals 12 years through 17 years of age not previously vaccinated with any COVID-19 vaccine was inferred based on a comparison of immune responses in this age group with immune responses in individuals 18 years through 25 years of age not previously vaccinated with any COVID-19 vaccine and a supportive descriptive efficacy analysis (see Section 6.2.4 of the Decision Memorandum).

Effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine was demonstrated based upon a comparison of immune responses following a 3rd dose with immune responses following a 2-dose series in individuals 18 years of age and older not previously vaccinated with any COVID-19 vaccine (see Section 6.4 of the Decision Memorandum).

Effectiveness data submitted to the EUA amendment to support a single-dose regimen in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine include the following:

- **Study 2019nCoV-301 pediatric extension (Study 301 pediatric extension):** In Study 301, neutralizing antibody responses against the ancestral (Wuhan) pseudovirus induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) at Day 28 post-Dose 3 and at Day 14 post-Dose 2 were compared in adolescents 12 years through 17 years of age who received a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) followed by a 3rd dose at least 5 months after completion of the 2-dose series(reviewed in Section 6.2.3). Noninferiority criteria were met for neutralizing antibody responses, by GMTR, and by percentage difference in seroconversion rates (SCRs).

2023-2024 Formula strain update

Effectiveness data that support the strain change to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) as a single-dose regimen in individuals 18 years of age and

older previously vaccinated with any COVID-19 vaccine include the following:

- **Study 2019nCoV-311 Part 2 (Study 311 Part 2):** In individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine, neutralizing antibody responses against a Omicron BA.5 pseudovirus induced by a single-dose regimen of NVX-CoV2540, hereafter referred to as monovalent vaccine (Omicron BA.5), were compared with neutralizing antibody responses against the Omicron BA.5 pseudovirus induced by a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (reviewed in Section 6.2.1). In this analysis, the superiority success criterion was met for geometric mean titer ratio (GMTR) and the noninferiority success criterion was met for the percentage difference in seroresponse rates (SRRs). Noninferiority criteria were also met for neutralizing antibody responses by GMTR and percentage difference in SRRs against the ancestral (Wuhan-Hu-1) strain induced by a single-dose regimen of monovalent vaccine (Omicron BA.5) compared with a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine.

- **Study 2019nCoV-311 Part 1 (Study 311 Part 1):** In individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine, neutralizing antibody responses against the Omicron BA.1 virus induced by a single-dose regimen of NVX-CoV2540, hereafter referred to as monovalent vaccine (Omicron BA.1), were compared with neutralizing antibody responses against the Omicron BA.1 virus induced by a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (reviewed in Section 6.2.2). In this analysis, the superiority success criterion was met for by geometric mean titer ratio (GMTR) and the noninferiority success criterion was met for the difference in seroresponse rates (SRRs). Noninferiority criteria were also met for neutralizing antibody responses by GMTR and percentage difference in SRRs against the ancestral (Wuhan-Hu-1) strain induced by a single-dose regimen of monovalent vaccine (Omicron BA.1) compared with a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine.

Effectiveness data that support the strain change to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) as a 2-dose series in individuals 12 years of age and older not previously vaccinated can be extrapolated from the superior neutralizing antibody responses (as measured by GMTR) and noninferior percentage difference of SRRs induced by monovalent vaccine (Omicron BA.5) and monovalent vaccine (Omicron BA.1), each compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) demonstrated in **Study 2019nCoV-311 Part 1 and Part 2 (**reviewed in Sections 6.2.2 and 6.2.1).

Based on the accumulated efficacy and immunogenicity data and because Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is manufactured using a similar process and the same antigen and adjuvant dose as monovalent vaccine (Omicron BA.5) and monovalent vaccine (Omicron BA.1), it is reasonable to expect that a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older not previously vaccinated with a COVID-19 vaccine and a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently

predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

The same expectation is reasonable for a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age not previously vaccinated with a COVID-19 vaccine and a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine, based on a) noninferior neutralizing antibody responses post-Dose 3 in previously vaccinated individuals compared with post-Dose 2 in previously unvaccinated individuals 12 years through 17 years of age, and b) extrapolation of the superior neutralizing antibody responses to the modified monovalent vaccines from individuals 18 years of age and older to individuals 12 years through 17 years of age in the context of previously reviewed comparable efficacy and immunogenicity results between these two age groups observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum).

Novavax COVID-19 Vaccine, Adjuvanted (2023-2024) Safety

The total safety database for all Novavax COVID-19 vaccine, adjuvanted includes approximately 45,000 participants who received at least one dose of vaccine at the authorized dose level. Approximately 28,500 individuals received at least one dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), approximately 1,000 individuals received at least one dose of monovalent or bivalent vaccine containing spike proteins of SARS-CoV-2 Omicron variants, and approximately 15,000 individuals received at least one dose of a formulation of the original monovalent vaccine that was manufactured using a different manufacturing process.

Safety of a 2-dose series and a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) has been previously described in individuals 18 years of age and older (see Section 6.2.5 of the Decision Memorandum and Section 6.5 of the Decision Memorandum) and in a 2-dose series in individuals 12 years through 17 years of age (see Section 6.2.5 of the Decision Memorandum).

Safety data submitted to the EUA amendment to support the strain change to the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) as a 2-dose series in individuals 18 years of age and older not previously vaccinated with a COVID-19 vaccine and as a single-dose regimen in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine include the following:

- **Study 2019nCoV-311 Part 1 and Part 2:** Novavax COVID-19 Vaccine, Adjuvanted formulations evaluated in Study 311 Part 1 and Part 2 were well tolerated with an acceptable safety profile when administered as a single-dose regimen in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine (see Sections 6.2.2 and 6.2.1). The local and systemic reactogenicity data were consistent with the known safety profile of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum). In Study 301 Part 2, two related SAEs of oculomotor cranial nerve palsy were reported in close temporal relationship to the single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted in previously COVID-19 vaccinated adult participants. In addition to inclusion of these events in product labeling (see Fact Sheet), this potential safety signal will be addressed via enhanced pharmacovigilance in postmarketing. No other new safety concerns were identified based on review of the safety data from Study 311 Part 1 and Part 2.

Safety data submitted to the EUA amendment to support a single-dose regimen in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine include the following:

- **Study 2019nCoV-301 pediatric extension:** Following a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine had higher numbers of fevers (greater than 2 times higher as those reported in individuals 18 years of age and older), nausea or vomiting, and headaches, consistent with increased reactogenicity in this age group (see section 6.2.3). Individuals 12 years through 17 years of age had substantially higher rates of grade 3 local and solicited systemic adverse reactions with each succeeding dose of vaccine with the percentage of subjects reporting grade 3 reactions for injection site reaction, pain/ tenderness, any systemic reaction, fever, fatigue/malaise, myalgia, arthralgia and headache, approximately 3-5 times higher with Dose 2 compared with Dose 1 and ten times higher with Dose 3 compared with Dose 1.

Data from Study 311 Parts 1 and 2 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) strain change for all age groups and regimens because these vaccines are manufactured using a similar process and contain the same amounts of antigen and adjuvant as Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Although there are no clinical safety data for the modified vaccine formulations in individuals 12 years through 17 years of age, it is reasonable to expect a similar safety profile for Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in this age group compared with individuals 18 years of age and older, as (1) the safety profiles for the modified vaccines were comparable to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in Study 311 Part 1 and 2, and (2) the general safety profile for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) has been comparable between individuals 18 years of age and older and individuals 12 years through 17 years of age based on the available clinical data.

An independent study conducted in the United Kingdom (ISRCTN 73765130), which demonstrated an increased immune response to a single dose of Novavax COVID 19 Vaccine, Adjuvanted (Original monovalent) administered at a median of 105 days (range: 93-147 days) after completion of a 2-dose series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), was considered in the totality of evidence supporting a minimum interval of 2 months for a single-dose regimen with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older (see Section 7.1 of the Decision Memorandum).

Given that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is manufactured using a similar process as Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), postmarketing safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) were considered relevant to the safety evaluation of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). According to the last update of COVID-19 vaccine administration data by CDC on May 10, 2023, 89,195 doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) have been administered in the U.S. In recipients of all doses of Novavax COVID-19 Vaccine, Adjuvanted among individuals aged 12 years of age and older, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) were dizziness, headache, fatigue, chest pain, dyspnea, pain, nausea,

pyrexia, myalgia, and paraesthesia. For important risks identified in the pharmacovigilance plan for Novavax COVID-19 Vaccine, Adjuvanted, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting a safety-related post-authorization study for Novavax COVID-19 Vaccine, Adjuvanted, to evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to Section 7 for details).

Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) Nonclinical Effectiveness

The nonclinical data reviewed indicate that Novavax Vaccine (2023-2024 Formula), when used in vaccine naïve or experienced laboratory animals, elicited higher neutralizing antibodies against XBB-related sublineages compared with the Novavax COVID-19 Vaccine (Original monovalent).

Conclusion

Based on the totality of the available evidence (reviewed in detail in Sections 6 and 7), it is reasonable to expect that in individuals 12 years of age and older that the Novavax COVID-19 Vaccine (2023-2024 Formula) compared with Novavax COVID-19 Vaccine (Original monovalent) will likely increase immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages.

Recommendation

Based on the accumulated safety, immunogenicity, efficacy, and nonclinical data the review team recommends: 1) discontinuation of use of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the U.S.; and 2) use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older, with an appropriate dosing schedule based on previous vaccination status.

2 Background

2.1 SARS-CoV-2 Virus and COVID-19

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. As of September 21, 2023, SARS-CoV-2 infection has resulted in over 770 million cases of COVID-19 and an estimated 7 million deaths worldwide.[4] 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,[5] 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.[6] 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.[7,8] 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.[9]

In the U.S., more than 6.3 million COVID-19-associated hospitalizations and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[10] Individuals 65 years of age and older accounted for approximately 14% of cases and 76% of deaths.[11] By

contrast, individuals 18 years of age and younger represent 17% of COVID-19 cases and less than 0.3% of deaths.[11] 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 or reference 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.

The SARS-CoV-2 Omicron variant has 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 post-vaccination (with Original strain vaccines) and post-infection sera compared to the 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 post-vaccination 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.

XBB sublineages have continued to emerge that have accumulated a small number of mutations in the spike N-terminal domain and the receptor binding domain (RBD). The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world, by April. Compared to the parental XBB lineage virus, XBB.1.5 has two amino acid substitutions, G252V and S486P, in the RBD of the SARS-CoV-2 spike protein. These changes may confer additional growth advantage, likely due in part to increased affinity of the spike protein to the ACE2 receptor conferred by the S486P change.[12] Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5. The XBB.1.9 variant has the same spike protein sequence as XBB.1.5, but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness. [13,14] Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April 2023 the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared with the parental XBB lineage virus, XBB.1.16 has four spike substitutions, i.e., E180V, G252V, K478R, and S486P. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses rose rapidly in many other countries, including the U.S. Preliminary reports have indicated that no further immune evasion result from these substitutions in the XBB.1.16 spike protein compared with XBB.1.5.[15,16] Overall, XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023;

at this time (August 2023), other circulating variants worldwide include 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 mid-September 16, 2023 was EG.5. EG.5 carries an additional F456L amino acid substitution in the spike protein compared to the parent XBB.1.9.2 subvariant and XBB.1.5.[17] Within the EG.5 lineage, the subvariant EG.5.1 has an additional spike protein substitution Q52H and represents 88% of the available sequences for EG.5 and its descendent lineages.[18]

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.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

Two COVID-19 vaccines are currently FDA approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 for use in individuals 12 years of age and older. Three vaccines are currently authorized for use in the U.S. under emergency use authorization (EUA).

2.2.1 Comirnaty and Pfizer-BioNTech Vaccine (2023-2024 Formula)

Comirnaty (COVID-19 Vaccine, mRNA) (2023-2024 Formula), manufactured by Pfizer for 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. Comirnaty contains a mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), is currently authorized under EUA for administration of a single dose in individuals 5 years through 11 years of age irrespective of COVID-19 vaccination status, three doses (Dose 1: Week 0, Dose 2: Week 3; Dose 3: ≥8 weeks after Dose 2) in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two doses (Dose 1: 3 weeks after receipt of previous dose; Dose 2: ≥8 weeks after Dose 1) if previously vaccinated with a dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), or a single dose administered ≥8 weeks in individuals 6 months through 4 years of age previously vaccinated with two to four doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). In individuals 6 months through 11 years of age with certain kinds of immunocompromise, an age-appropriate dose and dosing schedule of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is currently authorized, where unvaccinated individuals receive a three-dose series and individuals previously vaccinated with one or two doses Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) receive age-appropriate doses to complete the three-dose series. Additional age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine, (2023-2024 Formula) are authorized for individuals with certain kinds of immunocompromise 6 months through 11 years of age. For details, refer to Fact Sheet for Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

2.2.2 Spikevax and Moderna COVID-19 Vaccine (2023-2024 Formula)

Spikevax (COVID-19 Vaccine, mRNA), (2023-2024 Formula) manufactured by Moderna, 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. Spikevax contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized full-length spike (S) protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). Moderna COVID-19 Vaccine (2023-2024 Formula), is currently authorized under EUA for administration of a single dose in individuals 5 years through 11 years of age irrespective of COVID-19 vaccination status, two doses given one month apart in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, a single dose administered one month after receipt of a previous dose of Moderna COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), or a single dose administered at least 2 months after the receipt of two or more doses of Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). In individuals 6 months through 11 years of age with certain kinds of immunocompromise Moderna COVID-19 Vaccine (2023-2024 Formula) is currently authorized, where unvaccinated individuals receive a three-dose series and individuals previously vaccinated with one or two doses of Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) receive appropriate doses to complete the three-dose series. Additional age-appropriate doses of Moderna COVID-19 Vaccine, (2023-2024 Formula) are authorized for individuals with certain kinds of immunocompromise 6 months through 11 years of age. For details, refer to Fact Sheet for Moderna COVID-19 Vaccine (2023-2024 Formula)

2.2.3 Novavax COVID-19 Vaccine, Adjuvanted

Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is currently authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older, and as a first booster dose in the following individuals: Individuals 18 years 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. For additional information on dosing and schedule, please refer to the Fact Sheet. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.4 Therapies for COVID-19

2.2.4.1 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 extracorporeal membrane oxygenation (ECMO).

2.2.4.2 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 authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) 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 (IMV), 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.

3 Rationale for Strain Change

3.1 Current Effectiveness of Authorized COVID-19 Vaccines and Need for a Strain Update

Following emergence of the Omicron variant and its sublineages (BA.1, BA.4/BA.5, and related sublineages) in November 2021, and based on immunogenicity data suggesting improved protection against Omicron sublineages conferred by bivalent COVID-19 vaccines (Original and Omicron BA.1) compared with the monovalent original COVID-19 vaccines, in 2022 FDA authorized use of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines (manufactured by Pfizer-BioNTech Inc., and ModernaTx Inc.) for booster doses in children and adults and revised the scope of authorization for these manufacturers' original monovalent vaccines to remove their use in the U.S. as a booster dose in all age groups.

Subsequent to the authorizations of the bivalent mRNA COVID-19 vaccines as boosters in children and adults, observational data indicated that the bivalent COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage, compared to the original monovalent vaccines.[19-25] The improved protection against circulating variants provided by the bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines compared with the monovalent original COVID-19 vaccines provided supported for the use of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines for all doses for mRNA COVID-19 vaccines authorized in individuals 6 months of age and older as well as provided support for periodic updates of the strain composition of COVID-19 vaccines.

SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations (see Section 2.1). COVID-19 vaccines available in the U.S., have retained some level of effectiveness against circulating sublineages of Omicron, including XBB.1.5, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.[2,3,26-36] However, there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time.[3]

Recent epidemiology data indicate that SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations. By mid-September 2023, Omicron XBB-lineage descendants account for >95% of the currently circulating SARS-CoV-2 sublineages in the U.S. (See section 2.2). To ensure that COVID-19 vaccines remain effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages, an update to the strain composition of COVID-19 vaccines to match more closely the currently circulating Omicron sublineages is warranted.

3.2 Recommendation for the 2023-2024 Formula of COVID-19 Vaccines in the United States

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. At the January 26, 2023, VRBPAC meeting on COVID-19

vaccines, FDA stated that it anticipates assessing SARS-CoV-2 evolution at least annually (review of data to commence in the Spring of each year) and to convene the VRBPAC in June of each year regarding strain selection for fall vaccination.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the U.S. as of early June 2023. While XBB.1.5 had declined to less than 40% of presumed circulating virus in the U.S., XBB.1.16 was on the rise and XBB.2.3 was slowly increasing in proportion (CDC COVID Data Tracker: Variant Proportions).[17] The trajectory of virus evolution suggested that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolved. Although SARS-CoV-2 continues to evolve, the amino acid sequences of XBB.1.5, XBB.1.16, and XBB.2.3 spike protein appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new amino acid substitutions in the XBB.1.16 spike protein compared to XBB.1.5. The totality of available evidence suggests that an update to the composition of COVID-19 vaccine to a monovalent XBB-lineage vaccine is warranted for 2023–2024.

The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. Sublineages considered by the VRBPAC included XBB.1.5, XBB.1.16, and XBB.2.3. Evidence influencing strain selection discussed by the Committee included virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, pre-clinical immunogenicity studies evaluating immune responses generated by candidate vaccines. The Committee also reviewed manufacturing timelines.

For the 2023-2024 Formula of COVID-19 vaccines in the U.S., the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage. Based on the evidence and other considerations presented, committee members expressed a preference for selection of XBB.1.5 for the 2023-2024 Formula. Based on the totality of the evidence, FDA advised manufacturers seeking to update their COVID-19 vaccines that for the 2023-2024 Formula of COVID-19 vaccines in the U.S. they should develop vaccines with a monovalent XBB.1.5 composition.

4 Regulatory Considerations for EUA of a COVID-19 Vaccine with an Omicron Component

4.1 U.S. Requirements to Support Issuance of an EUA for a Biological Product

The Secretary of the U.S. Department of Health and Human Services (HHS) has determined that there is a public health emergency or a significant potential for a public health emergency, that affects, or has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. Based on that determination, and the Secretary's declaration that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, FDA may issue an EUA after determining that certain statutory requirements are met [section 564 of the FD&C Act (21 U.S.C. 360bbb-3)].

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-

controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency expectations.

4.2 FDA Guidance for Industry Related to COVID-19 Vaccines, Including Modified COVID-19 Vaccines

Appendix 2 of the FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (originally issued in October 2020 and last updated March 2022) discusses an approach to CMC, nonclinical and clinical data to support the safety and effectiveness of a modified monovalent vaccine to address emerging SARS-CoV-2 variants. With respect to clinical data, the guidance recommends clinical evaluation of modified monovalent vaccines, while also recognizing that FDA's thinking regarding data needed to authorize a modified COVID-19 vaccine may evolve as additional information is accrued with SARS-CoV-2 variants and corresponding vaccines. Although the authorization of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is not supported by clinical studies of the 2023-2024 formula vaccine, FDA's thinking about the need for such data has evolved since issuance of the guidance. Based upon the accumulated experience with the Novavax COVID-19 Vaccine, Adjuvanted (Original, monovalent) as well as clinical studies of investigational Novavax COVID-19 Vaccine, Adjuvanted formulations, including monovalent vaccine (Omicron BA.5), monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.4/BA.5), and bivalent vaccine (Original and Omicron BA.1) (see Section 6), it is reasonable to conclude that clinical studies of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) are not necessary to support issuance of an EUA for the 2023-2024 Formula. The experience with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), combined with the CMC, clinical, and preclinical data submitted as part of the 2023-2024 Formula EUA request, support a favorable benefit-risk profile for the uses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) that are under consideration.

5 EUA Amendment Request to Include the 2023-2024 Formula for Novavax COVID-19 Vaccine, Adjuvanted

5.1 Summary of the EUA Request

Following the June 15, 2023, VRBPAC discussion and FDA's advice to manufacturers updating

their vaccines to develop vaccines with a monovalent XBB.1.5 composition (Section 3.2), Novavax submitted a request on September 6, 2023, to amend the EUA of their COVID-19 Vaccine, Adjuvanted, to include a monovalent Omicron XBB.1.5 subvariant vaccine (2023-2024 Formula) for individuals 12 years of age and older as a 2-dose series in individuals not previously vaccinated with any COVID-19 vaccine and as a single dose for individuals previously vaccinated at least 2 months after receipt of the last previous dose of any original monovalent and/or bivalent COVID-19 vaccine based upon:

- Preclinical data that support the strain selection.
- CMC Information supporting the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula).
- Clinical data from the following studies in support of the safety and inferred effectiveness of the dosing regimen and strain change under consideration:
    - Study 2019nCoV-311 (referred to as Study 311) Part 1 evaluates the safety and immune responses generated by a single dose of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and compared with the bivalent vaccine (Original and Omicron BA.1).
    - Study 311 Part 2 evaluates the safety and immune responses generated by a single dose of the monovalent vaccine (Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and compared with the bivalent vaccine (Original and Omicron BA.5)
    - Pediatric Extension of Study 2019nCoV-301 (referred to as Study 301) evaluates the efficacy, safety, and immunogenicity of a single dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

5.2 FDA's Approach for Selection of Strains to be Included in 2023-2024 Formula for COVID-19 Vaccines

In previous discussions with the VRBPAC, FDA described the proposed evidentiary basis that would be used to determine the need for updating the strain composition of COVID-19 vaccines. The relevant data reviewed would ideally include multiple types and sources. FDA reviewed various types of data as listed below, engaged with the key partners generating such data, including vaccine manufacturers and other U.S. government agencies, and reviewed the discussions and recommendations by other regulatory groups and public health agencies related to COVID-19 vaccine strain composition for 2023-2024.

- **Virus surveillance and genomic analyses to identify emerging new virus variants**. As described in Section 2.1, SARS-CoV-2 XBB-lineage viruses currently predominate in the U.S. and globally.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses**. As described in Section 2.1, SARS-CoV-2 XBB-lineage viruses have numerous amino acid changes relative to previously circulating SARS-CoV-2 viruses and the strains used in the bivalent mRNA COVID-19 vaccines (previously, but no longer authorized for use in the U.S.), suggesting continued evolution and increasing immunological distance from the Omicron BA.4/BA.5 component of those COVID-19 vaccines.

- **Post-vaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants such as XBB-lineage viruses**. Since COVID-19 vaccine manufacturers are best positioned to generate the robust data needed from post-vaccination human serology studies, FDA set up informal technical working group meetings with each of the manufacturers of currently authorized/approved COVID-19 vaccines to share and discuss findings from human serology studies of their current vaccines against current circulating viruses. These data were presented at the June 2023 VRBPAC by the vaccine manufacturers.
- **Pre-clinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant spike components) against antigenically distinct circulating virus variants**. Pre-clinical immunogenicity data (neutralizing antibody) can provide an indication of how well antibodies to the spike protein of one strain will cross-neutralize other variant strains of SARS-CoV-2. These data help inform strain selection in combination with other data. As with human serology studies, COVID-19 vaccine manufacturers are also able to generate pre-clinical immunogenicity studies with new candidate vaccines and each of the manufacturers of authorized/approved COVID-19 vaccines has produced several candidate vaccines at risk and evaluated them in pre-clinical studies. These data were also presented at the June 2023 VRBPAC by the vaccine manufacturers.

5.3 Basis for EUA Revision to Remove Authorization for Use of Novavax COVID-19 Vaccine, Adjuvated (Original monovalent) in the U.S. and Clarify Export and Other Conditions

FDA may revise or revoke an EUA if the circumstances justifying its issuance (under section 564(b)(1) of the FD&C Act) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety (see section 564(g)(2) of the FD&C Act).

Circumstances currently exist that make appropriate a revision of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) EUA to protect the public health. As outlined in Section 2.2, the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is authorized for use in individuals 12 years of age and older. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), for individuals 12 years of age and older, as described in the EUA request, is being considered for the purpose of improving protection against the currently circulating SARS-CoV-2 Omicron sublineages, resulting in a more favorable anticipated benefit-risk profile for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). In addition, revising the EUA to remove the authorization of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for use in the U.S. ensures that vaccination programs will continue to use a single current formula (i.e., 2023-2024 Formula) for Novavax COVID-19 Vaccine, Adjuvanted, which should continue to help minimize vaccine administration errors that would result from availability of multiple different vaccine formulas and also potentially encourage vaccine uptake. Consequently, at this time, revising the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) EUA to remove its authorization for use in the U.S. is appropriate to protect the public health.

That said, the considerations about the U.S. vaccination programs are not applicable when the vaccine is used in other countries, and existing supplies of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted

(Original monovalent) outweigh the known and potential risks, when used consistent with the current authorization. In addition, all other requirements in section 564(c) of the FD&C Act continue to be met with respect to the uses for which the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) is currently authorized. Therefore, it is appropriate to continue to authorize the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for export.

Accordingly, authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for use in 12 years of age and older as described in the EUA request, would be accompanied by the revision of the authorization for the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to remove its authorization for use in the U.S. in individuals 12 years of age and older but permit its continued export under the EUA, subject to specific conditions. These conditions include, among other things, that the regulatory authorities of the countries in which the vaccine will be used are informed that Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and associated Fact Sheets are no longer authorized for use in the U.S. and that FDA is no longer revising those Fact Sheets with updated information. These conditions also include a requirement to provide the regulatory authorities, upon request, with the currently authorized Fact Sheets. These conditions will ensure that the regulatory authorities in destination countries have relevant information with respect to the vaccine.

Previously, FDA's EUA required the distribution of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to emergency response stakeholders at the direction of the U.S. government as a condition necessary or appropriate to protect the public health. Due to changed circumstances, we conclude that this limitation on distribution is no longer necessary or appropriate to protect the public health. Whereas there was previously a need for the U.S. government to coordinate distribution across federal, state, and local government entities to ensure appropriate allocation of COVID-19 vaccines, this is no longer the case. In addition, we are no longer requiring all vaccination providers administering COVID-19 vaccine to be enrolled in the CDC COVID-19 Vaccination Program, as CDC no longer plans for that program to apply to all vaccination providers and this requirement is no longer necessary or appropriate to protect the public health.

6 FDA Review of Clinical Effectiveness and Safety Data

6.1 Overview of Clinical Studies

The safety and effectiveness of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is supported by data from administration of a 2-dose series and administration of a 3rd dose in a large clinical efficacy trial of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adults and adolescents (Study 301). Additionally, safety and immunogenicity data following administration of a single dose of monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.1), and monovalent vaccine (Omicron BA.5), and bivalent vaccine (Original and Omicron BA.5) (Study 311 Part 1 and 2, respectively) in previously vaccinated adults support the clinical effectiveness and safety of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) because these vaccines share the same platform, dose of antigen (5 µg total) and Matrix-M adjuvant (50 µg), and are manufactured using a similar process.

6.1.1 Effectiveness of a 2-Dose Series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in Individuals 12 Years of Age and Older Not Previously Vaccinated With a COVID-19 Vaccine

The effectiveness of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) as a 2-

dose series in individuals 12 years of age and older ***not previously vaccinated*** with a COVID-19 vaccine is based on the following evidence by age group:

- 18 years of age and older
  - 2-dose series: Previously reviewed data for a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) from Study 301, which demonstrated vaccine efficacy of 90.4% (95% CI: 83.8%, 94.3%) to prevent polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate or severe COVID-19 from 7 days after Dose 2 (see Section 6.2.4 of the Decision Memorandum).
  - 2023-2024 Formula (strain change): Immunogenicity data from Study 311 Parts 1 and 2 comparing neutralizing antibody responses following a "booster" dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) with neutralizing antibody responses following a "booster" dose of one of the four modified Novavax COVID-19, Vaccine, Adjuvanted formulations (Part 1: monovalent vaccine [Omicron BA.1], and bivalent vaccine [Original and Omicron BA.1]; and Part 2: monovalent vaccine [Omicron BA.5] and bivalent [Original and Omicron BA.5], which demonstrate superior immune responses to the respective Omicron sublineage component of each vaccine and noninferior immune responses to the Original strain component of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (descriptive for monovalent [Omicron BA.5] and bivalent [Original and Omicron BA.1]) (reviewed below in Sections 6.2.1 and 6.2.2).
- 12 years through 17 years of age
  - 2-dose series: Previously reviewed data for a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) based on a comparison of immune responses in this age group with adults 18 years through 25 years of age, and a supportive descriptive efficacy analysis (see Section 6.2.4 of the Decision Memorandum).
  - 2023-2024 Formula (strain change): Extrapolation from immunogenicity data in adults from Studies 311 Part 1 and Part 2 (described above and reviewed below in Sections 6.2.1 and 6.2.2), 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) (see Section 6.2.4 of the Decision Memorandum).

6.1.2 Effectiveness of a Single-Dose Regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in Individuals 12 Years of Age and Older Previously Vaccinated With a COVID-19 Vaccine

The effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older ***previously vaccinated*** with an original monovalent or bivalent COVID-19 vaccine is based on the following evidence:

- 18 years of age and older
  - Single-dose regimen (previous homologous vaccination): Previously reviewed data from Study 301 for a 3rd dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) following a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), which demonstrated comparable immune responses following the 3rd dose with immune responses following a 2-dose series (see Section 6.4 of

the Decision Memorandum).

- Single-dose regimen (previous heterologous vaccination): Previously reviewed data for a single dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) following a 2-dose series with another authorized or approved COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine) from an independent study conducted in the United Kingdom (ISRCTN 73765130), which demonstrated an increased immune response to the Novavax COVID 19 Vaccine, Adjuvanted (Original monovalent) (see Section 7.1 of the Decision Memorandum).
- 2023-2024 Formula (strain change): Immunogenicity data from Study 311 Parts 1 and 2 comparing neutralizing antibody responses following a "booster" dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) with neutralizing antibody responses following a "booster" dose of one of the modified Novavax COVID-19, Vaccine, Adjuvanted formulations [(i.e., Part 1: monovalent vaccine (Omicron BA.1), and bivalent vaccine (Original and Omicron BA.1); and Part 2: monovalent vaccine (Omicron BA.5) and bivalent (Original and Omicron BA.5)], which demonstrate superior immune responses to the respective Omicron sublineage component of each vaccine and noninferior immune responses to the Original strain compared with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) immune responses (descriptive for monovalent [Omicron BA.5] and bivalent [Original and Omicron BA.1]) (reviewed below in Sections 6.2.1 and 6.2.2).

- 12 years through 17 years of age
  - Single-dose regimen (previous homologous vaccination): Immunogenicity data in this age group from Study 301, which demonstrated neutralizing antibody responses after a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age who were previously vaccinated with a COVID-19 vaccine that were comparable with a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age who were previously not vaccinated with a COVID-19 vaccine (reviewed below in Section 6.2.3).
  - Single-dose regimen (previous heterologous vaccination): Extrapolation from previously reviewed data for a single dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) following a 2-dose series with another authorized or approved COVID-19 vaccine (Pfizer-BioNTech COVID-19 Vaccine) in adults (see above and Section 7.1 of the Decision Memorandum), 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) (see Section 6.2.4 of the Decision Memorandum).
  - 2023-2024 Formula (strain change): Extrapolation from a single dose immunogenicity data in previously vaccinated adults from Studies 311 Part 1 and Part 2 (described above and reviewed below in Sections 6.2.1 and 6.2.2), 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) (see Section 6.2.4 of the Decision Memorandum).

6.1.3 Safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older

The safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older is based on the following evidence:

- 2-dose series in previously unvaccinated: Previously reviewed safety data from Study 301 following administration of a two-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in participants 12 years of age and older (see 6.2.5 in the Decision Memorandum for 18 years of age and older and the Decision Memorandum for 12 to 18 years of age).
- Single-dose regimen in previously vaccinated adults: Previously reviewed safety data from Study 301 following administration of a 3rd dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in participants 18 years of age and older (see Section 6.5 of the Decision Memorandum).
- Single-dose regimen in previously vaccinated adolescents (12 years through 18 years of age): Safety data from Study 301 following administration of a single booster of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in participants 12 years through 18 years of age (reviewed below in Section 6.2.3).
- 2023-2024 Formula (strain change): Safety data in participants 18 years of age and older from Study 311 Parts 1 and 2 administered modified Novavax COVID-19 vaccine formulations [i.e., Part 1: monovalent vaccine (Omicron BA.1) and bivalent vaccine (Original and Omicron BA.1); and, Part 2: monovalent vaccine (Omicron BA.5) and bivalent vaccine (Original and Omicron BA.5)] (reviewed below in Sections 6.2.1 and 6.2.2).
- Dosing interval for single-dose regimen in previously vaccinated: Minimum interval of 2 months for a single-dose regimen with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in previously vaccinated individuals 12 years of age and older from an independent study conducted in the United Kingdom (ISRCTN 73765130). This study demonstrated an increased immune response to a single dose of Novavax COVID 19 Vaccine, Adjuvanted (Original monovalent) administered at a median of 105 days (range: 93-147 days) after completion of a 2-dose series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) was considered in the totality of evidence supporting and older (see Section 7.1 of the Decision Memorandum).
- Postmarketing safety: Accrual of safety signals from post-authorization surveillance of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (reviewed below in Section 7.5) [**N.B.** Although over 1.5 million doses of Novavax COVID-19 Vaccine, Adjuvanted have been *distributed* in the U.S., less than 90 thousand doses of Novavax COVID-19 Vaccine, Adjuvanted had been *administered* in the U.S., as of the last CDC update on May 10, 2023.]

6.2 Clinical Studies

6.2.1 Study 311 Part 2

The sections below summarize interim immunogenicity and safety data from ongoing Study 311 Part 2, in which participants who had been 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) were randomized to receive Novavax COVID-

19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), or bivalent (Original and Omicron BA.5). Each vaccine included a total of 5 µg of antigen and 50 µg of Matrix-M adjuvant. The interim analysis includes data collected through a median of 70 days in 766 participants.

6.2.1.1 Study Design: Study 311 Part 2

Study 311 Part 2 was originally designed with a primary objective to compare the immune responses following a "booster" dose of the bivalent (Original and Omicron BA.5) with those following a "booster" dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). Study 311 Part 2 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 EUA request. The FDA immunogenicity analyses also include review of Study 311 Part 2 secondary endpoints, which evaluated neutralizing antibody immune responses against the ancestral (Wuhan) sublineage. See additional details in the section below entitled "Immunogenicity Statistical Analysis Plan."

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 to 54 years of age and ≥55 years of age). Although Study 311 Part 2 was originally designed to administer 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. Data from the second dose administered on Day 90 are not included in this review.

Blood samples for immunogenicity assessments were collected and analyzed before vaccination on Day 0 and on Days 14 and 28 post-single-dose regimen. To characterize the immune response generated by each of the 3 study vaccines, blood samples were analyzed for Omicron BA.5 sublineage and ancestral (Wuhan) strain 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 BA.5 sublineage-specific, ancestral (Wuhan) strain-specific, and XBB.1.5 sublineage-specific neutralizing antibody titers.

<u>Immunogenicity Population</u>
Available immunogenicity data at the time of interim study analysis were from randomized participants who received 1 dose of study vaccine through the data extraction date of June 22, 2023. 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).

Immunogenicity Statistical Analysis Plan

Immune responses following a single dose of the monovalent vaccine (Omicron BA.5) and a single dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) were assessed descriptively using the following exploratory endpoints at 28 days post-vaccination:

- Neutralizing antibody GMTs against the BA.5 sublineage
- Seroresponse rates (SRRs) against the BA.5 sublineage
- Neutralizing antibody GMTs against the ancestral (Wuhan) strain
- SRRs against the ancestral (Wuhan) strain

The above exploratory endpoints were used to compare the monovalent vaccine (Omicron BA.5) with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) 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.

As described above, the study was originally designed to compare immune responses to the bivalent vaccine (Original and Omicron BA.5) with those following the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) using the following 3 co-primary endpoints:

1. Superiority of the bivalent vaccine (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for neutralizing antibody GMTs generated against the Omicron BA.5 sublineage. Criterion for superiority is met if the 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) is greater than 1.0.

2. Noninferiority of the bivalent vaccine (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) by the percentage difference of SRRs for neutralizing antibodies to the Omicron BA.5 sublineage. Criterion for non-inferiority 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 (bivalent vaccine [Original and Omicron BA.5] minus Novavax COVID-19 Vaccine, Adjuvanted [Original monovalent]) is greater than -5%.

3. Noninferiority of the bivalent vaccine (Original and Omicron BA.5) 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 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) is >0.67, representing a 1.5-fold difference.

Similar success criteria as those described above were applied to these endpoints for the bivalent vaccine (Original and Omicron BA.5).

Safety Evaluation

Participants remained under observation for at least 30 minutes post-vaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants used an electronic diary (eDiary) to record solicited local and systemic reactogenicity events on the day of vaccination and for an additional 6 days after vaccination.

Unsolicited AEs were collected through 1 month post-vaccination. Collection of MAAEs, adverse events of special interest (AESIs), and serious AEs (SAEs) were planned through 8 months post-vaccination. Safety data through the data extraction date of June 22, 2023 were available for the interim study analysis, representing approximately 2 months of data collection post-vaccination.

AESIs included myocarditis/pericarditis, potential immune-mediated medical conditions (PIMMCs), and complications of COVID-19. Confirmed symptomatic cases of COVID-19 were recorded as adverse events, SAEs, or AESIs as appropriate.

Safety Analysis Population

Available safety data in the interim study analysis were reported for all randomized participants who received 1 dose of study vaccine through the data extraction date of June 22, 2023. Of the 766 randomized participants, 764 received a study vaccine, all of whom were included in the Safety Analysis Set.

Safety Statistical Analysis Plan

Adverse events were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA).

6.2.1.2 Demographics and Disposition: Study 311 Part 2

Participant Disposition

Of the 837 screened individuals, 766 were randomized to receive vaccination, and 10 (1.3%) had discontinued study participation as of the data extraction date of June 22, 2023. These discontinuations included 4 (1.6%) participants in the monovalent vaccine (Omicron BA.5) group, 3 (1.2%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 3 (1.2%) participants in the bivalent vaccine (Original and Omicron BA.5) group. The most common reason for discontinuation was participant decision to withdraw from the study. No participants withdrew from the study due to an adverse event.

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).

Immunogenicity Population

The evaluable immunogenicity population on Day 28 after vaccination (the per-protocol [PP] analysis set) was determined for those participants who completed testing for each pseudovirus and corresponding neutralization assay at the Day 28 study visit. For the Omicron BA.5

pseudovirus, the PP analysis set was comprised of 693 participants (90.5% of those randomized): 235 participants in the monovalent vaccine (Omicron BA.5) group, 227 in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 231 in the bivalent vaccine (Original and Omicron BA.5) group. For the Wuhan pseudovirus, the PP analysis set was also comprised of 693 participants (90.5% of those randomized): 236 participants in the monovalent vaccine (Omicron BA.5) group, 227 in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 230 in the bivalent vaccine (Original and Omicron BA.5) group. Participants in the PP Analysis Set received the full prescribed regimen of the study vaccine, were negative at baseline for SARS-CoV-2 infection by PCR testing, had no major protocol violations, and had serology results at baseline and on Day 28.

Safety Population

The evaluable safety population was comprised of all 764 vaccinated participants in the full analysis set (99.8% of those randomized). The median duration of safety follow-up time after study vaccination was 2 months (70 days).

Participant Demographics

Table 1 displays a summary of participant demographics and baseline disease characteristics in the Study 311 Part 2 Safety Analysis Set.

Table 1. Participant Demographics and Baseline Disease Characteristics, Safety Analysis Set

Parameter	Group F Monovalent (Omicron BA.5) N=254	Group G Original Monovalent N=251	Group H Bivalent (Original and Omicron BA.5) N=259
Age (years)	--	--	--
Mean (SD)	41.8 (12.89)	41.9 (13.58)	42.4 (12.48)
Median	43.0	43.0	43.0
Minimum-maximum	18-75	18-83	18-71
Age category, n (%)	--	--	--
18 to 54 years	211 (83.1)	209 (83.3)	212 (81.9)
≥55 years	43 (16.9)	42 (16.7)	47 (18.1)
Sex, n (%)	--	--	--
Male	113 (44.5)	111 (44.2)	120 (46.3)
Female	141 (55.5)	140 (55.8)	139 (53.7)
Race, n (%)	--	--	--
White	195 (76.8)	205 (81.7)	215 (83.0)
Black or African American	1 (0.4)	1 (0.4)	0
Aboriginal Australian	4 (1.6)	3 (1.2)	8 (3.1)
Native Hawaiian or other Pacific Islander	2 (0.8)	2 (0.8)	1 (0.4)
Asian	36 (14.2)	32 (12.7)	26 (10.0)
Mixed origin	6 (2.4)	0	1 (0.4)
Other	10 (3.9)	8 (3.2)	6 (2.3)
Not reported	0	0	2 (0.8)
Ethnicity, n (%)	--	--	--
Australian	220 (86.6)	221 (88.0)	224 (86.5)
Aboriginal/Torres Strait Islanders	5 (2.0)	5 (2.0)	7 (2.7)
Hispanic or Latino	5 (2.0)	3 (1.2)	8 (3.1)
Not reported	13 (5.1)	13 (5.2)	11 (4.2)
Unknown	11 (4.3)	8 (3.2)	7 (2.7)
Missing	0	1 (0.4)	2 (0.8)

Parameter	Group F Monovalent (Omicron BA.5) N=254	Group G Original Monovalent N=251	Group H Bivalent (Original and Omicron BA.5) N=259
BMI (kg/m^2)	--	--	--
n	252	250	256
Mean (SD)	28.59 (6.483)	28.76 (7.123)	28.48 (5.831)
Median	27.40	27.65	27.65
Minimum-maximum	16.9-59.4	16.2-70.6	16.0-51.8
BMI (kg/m^2) category, n (%)	--	--	--
Underweight (<18.0)	3 (1.2)	2 (0.8)	3 (1.2)
Normal (18.0-24.9)	79 (31.1)	85 (33.9)	75 (29.0)
Overweight (25.0-29.9)	83 (32.7)	73 (29.1)	85 (32.8)
Obese (≥30.0)	87 (34.3)	90 (35.9)	93 (35.9)
Missing	2 (0.8)	1 (0.4)	3 (1.2)
Previous COVID-19 Vaccine, n (%)	--	--	--
Yes	254 (100)	251 (100)	259 (100)
Regimen of Previous COVID-19 Vaccine, n (%)	--	--	--
3 doses	138 (54.3)	147 (58.6)	149 (57.5)
3 Moderna	5 (2.0)	1 (0.4)	2 (0.8)
3 Pfizer-BioNTech	108 (42.5)	109 (43.4)	121 (46.7)
1 Moderna + 2 Pfizer-BioNTech	24 (9.4)	36 (14.3)	26 (10.0)
2 Moderna + 1 Pfizer-BioNTech	1 (0.4)	1 (0.4)	0
4 doses	116 (45.7)	99 (39.4)	107 (41.3)
4 Moderna	0	1 (0.4)	0
4 Pfizer-BioNTech	72 (28.3)	53 (21.1)	66 (25.5)
1 Moderna + 3 Pfizer-BioNTech	33 (13.0)	28 (11.2)	24 (9.3)
2 Moderna + 2 Pfizer-BioNTech	11 (4.3)	17 (6.8)	17 (6.6)
3 Moderna + 1 Pfizer-BioNTech	0	0	0
5 doses	0	5 (2.0)	3 (1.2)
5 Moderna	0	0	0
5 Pfizer-BioNTech	0	4 (1.6)	2 (0.8)
1 Moderna + 4 Pfizer-BioNTech	0	1 (0.4)	1 (0.4)
2 Moderna + 3 Pfizer-BioNTech	0	0	0
3 Moderna + 2 Pfizer-BioNTech	0	0	0
4 Moderna + 1 Pfizer-BioNTech	0	0	0
Previous COVID-19, n (%)	--	--	--
Yes	13 (5.1)	14 (5.6)	18 (6.9)
No	**241 (94.9)**	**237 (94.4)**	**241 (93.1)**
Qualitative anti-N, n (%)	--	--	--
Positive	192 (75.6)	183 (72.9)	205 (79.2)
Negative	60 (23.6)	67 (26.7)	53 (20.5)
Missing	2 (0.8)	1 (0.4)	1 (0.4)
PCR, n (%)	--	--	--
Positive	7 (2.8)	5 (2.0)	5 (1.9)
Negative	247 (97.2)	246 (98.0)	254 (98.1)
Anti-N / PCR, n (%)[1]	--	--	--
Positive	**193 (76.0)**	**184 (73.3)**	**206 (79.5)**
Negative	61 (24.0)	67 (26.7)	53 (20.5)
Time Between Last Previous COVID-19 Vaccine and Booster Dose of Study Investigational Vaccine (Days)	--	--	--

Parameter	Group F Monovalent (Omicron BA.5) N=254	Group G Original Monovalent N=251	Group H Bivalent (Original and Omicron BA.5) N=259
Mean (SD)	349.0 (114.17)	352.9 (117.68)	358.4 (104.37)
Median	328.0	389.0	361.0
Minimum-maximum	103-679	87-626	103-537
Interval Between Last Previous COVID-19 Vaccine and Booster Dose of Study Investigational Vaccine, n (%)	--	--	--
<90 days	0	1 (0.4)	0
90-120 days	2 (0.8)	8 (3.2)	3 (1.2)
>120-150 days	7 (2.8)	6 (2.4)	5 (1.9)
>150-180 days	9 (3.5)	8 (3.2)	3 (1.2)
>180-210 days	6 (2.4)	7 (2.8)	7 (2.7)
>210-240 days	13 (5.1)	14 (5.6)	8 (3.1)
>240-270 days	46 (18.1)	31 (12.4)	41 (15.8)
>270-300 days	31 (12.2)	24 (9.6)	35 (13.5)
>300-330 days	13 (5.1)	16 (6.4)	19 (7.3)
>330-360 days	7 (2.8)	5 (2.0)	8 (3.1)
>360 days	120 (47.2)	131 (52.2)	130 (50.2)

Source: Study 311 Part 2 Interim Study Report, Table 8, p.35
Abbreviations: anti-N=anti-nucleocapsid; BMI=body mass index; COVID-19=coronavirus disease 2019; NVX-CoV2540=5 µg SARS-CoV-2 rS Omicron BA.5 subvariant with 50 µg Matrix-M adjuvant; NVX-CoV-2373=5 µg SARS-CoV-2 rS prototype Wuhan strain with 50 µg Matrix-M adjuvant; NVX-CoV2373 + NVX-CoV2540=5 µg SARS-CoV2 rS with 50 µg Matrix-M adjuvant (total); PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine; SD=standard deviation.
1. Participants with either anti-N or PCR are reported. 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 vaccine group (N).

Demographics and baseline disease characteristics were balanced across the 3 study vaccine groups. 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 and older. The majority of participants in each group were female (53.7% to 55.8%), 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).

6.2.1.3 Immunogenicity Results: Study 311 Part 2

Table 2 presents the 50% neutralizing antibody responses (ID_{50}) generated by the monovalent vaccine (Omicron BA.5) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the Omicron BA.5 pseudovirus.

Table 2. Summary of Serum Neutralizing Antibody Titers Against the Omicron BA.5 Pseudovirus Following Initial Study Vaccination, Per-Protocol Neutralization Assay Subset

Parameter	Group F Monovalent (Omicron BA.5) N=235	Group G Original Monovalent N=227	Group H Bivalent (Original and Omicron BA.5) N=231
Baseline	--	--	--
Pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	235	227	231
Median	391.0	392.0	348.0
Minimum-maximum	18-17214	18-33971	18-35387
GMT	346.0	326.6	293.3
95% CI	281.9, 424.9	260.0, 410.4	237.3, 362.6
Day 28	--	--	--
Pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	235	227	231
Median	1596.0	675.0	1263.0
Minimum-maximum	18-57888	18-38744	18-165841
GMT	1507.3	582.0	1068.1
95% CI	1259.0, 1804.5	476.3, 711.1	886.3, 1287.2
Adjusted GMT[1]	1279.1	515.1	1017.8
95% CI	1119.7, 1461.1	450.4, 589.0	891.0, 1162.6
GMFR between visit and baseline	--	--	--
n2	235	227	231
Reference to Day 0	4.4	1.8	3.6
95% CI	3.8, 5.1	1.6, 2.0	3.2, 4.2
Seroresponse from baseline	--	--	--
n3	107	28	92
Percentage	45.5	12.3	39.8
95% CI	39.0, 52.1	8.4, 17.3	33.5, 46.5

Source: Table 14.2.1.1.1 in the Study 311 Part 2 "14.2 Efficacy Data Summary Figures and Tables" submitted to EUA 28237.130
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inh bitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
N=number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set.
n1=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set within each visit with non-missing data.
n2=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set with non-missing data at both Day 0 and Day 28.
n3=Number of subjects achieving seroresponse.
1. 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.

Table 3 shows the following on Day 28 post-vaccination against the Omicron BA.5 pseudovirus:

Table 3. Comparison of Serum Neutralizing Antibody Titers Against the Omicron BA.5 Pseudovirus Following Initial Study Vaccination, Per-Protocol Neutralization Assay Subset

Comparison Between Groups	Monovalent (Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Original monovalent	Monovalent (Omicron BA.5) vs Bivalent (Original and Omicron BA.5)
GMTR[1]	2.5	2.0	1.3
95% CI	2.10, 2.94	1.69, 2.33	1.06, 1.50
Difference in SRRs[2], %	33.2	27.5	5.7
95% CI	25.4, 40.7	19.8, 35.0	-3.3, 14.6

Source: Table 14.2.1.1.1 in the Study 311 Part 2 "14.2 Efficacy Data Summary Figures and Tables" submitted to EUA 28237.130
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inh bitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
1. 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.
2. 95% CI for the percentage difference in SRRs is calculated based on the method of Miettinen and Nurminen.

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 with 95% confidence intervals: 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% with 95% confidence intervals: 25.4%, 40.7% (the lower limit of the 95% CI around the percentage difference in SRRs is >-5%).

Bivalent Vaccine (Original and Omicron BA.5) Primary Analysis:

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.5) versus Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against Omicron BA.5 sublineage was 2.0 with 95% confidence intervals: 1.69, 2.33, which met the superiority criterion (i.e., the lower limit of the 95% CI around the GMTR is >1).
- The estimated percentage difference in SRRs of the bivalent vaccine (Original and Omicron BA.5) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.5 sublineage was 27.5% with 95% confidence intervals: 19.8%, 35.0%, which met the noninferiority criterion (i.e., the lower limit of the 95% CI around the percentage difference in SRRs is >-5%).
- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.5) versus Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) vaccine against ancestral (Wuhan) pseudovirus was 1.0 with 95% confidence intervals: 0.84, 1.20, which met the noninferiority criterion (the lower limit of the 95% CI around the GMTR is >0.67), Table 5.

Table 4 presents the 50% neutralizing antibody responses (ID_{50}) generated by the monovalent vaccine (Omicron BA.5) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) pseudovirus.

Table 4. Summary of Serum Neutralizing Antibody Titers Against the Ancestral (Wuhan) Pseudovirus Following Initial Study Vaccination, Per-Protocol Immunology Subset

Parameter	Group F Monovalent (Omicron BA.5) N=236	Group G Original Monovalent N=227	Group H Bivalent (Original and Omicron BA.5) N=230
Baseline	--	--	--
Pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	236	227	230
Median	1591.5	1304.0	1327.0
Minimum-maximum	21-61325	21-28222	21-64197
GMT	1355.4	1259.7	1222.1
95% CI	1141.7, 1609.2	1044.1, 1519.8	1024.5, 1457.9
Day 28	--	--	--
Pseudovirus neutralizing antibody titers (ID_{50})	--	--	--
n1	236	227	230
Median	2233.5	2388.0	2138.5
Minimum-maximum	182-27263	65-122118	66-62861
GMT	2220.0	2337.7	2309.9
95% CI	1940.1, 2540.3	2007.5, 2722.2	1983.5, 2689.7
Adjusted GMT[1]	2020.2	2205.6	2211.1
95% CI	1766.6, 2310.1	1926.4, 2525.1	1932.9, 2529.3
GMFR between visit and baseline	--	--	--
n2	236	227	230
Reference to Day 0	1.6	1.9	1.9
95% CI	1.4, 1.9	1.6, 2.1	1.6, 2.2
Seroresponse from baseline	--	--	--
n3	53	52	54
Percentage	22.5	22.9	23.5
95% CI	17.3, 28.3	17.6, 28.9	18.2, 29.5

Source: Table 14.2.1.2.1 in the Study 311 Part 2 "14.2 Efficacy Data Summary Figures and Tables"
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inh bitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
N=number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set.
n1=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set within each visit with non-missing data.
n2=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set with non-missing data at both Day 0 and Day 28.
n3=Number of subjects achieving seroresponse.
1. 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.

Table 5. Comparison of Serum Neutralizing Antibody Titers Against the Ancestral (Wuhan) Pseudovirus Following Initial Study Vaccination, Per-Protocol Immunology Subset

Comparison Between Groups	Monovalent (Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Original Monovalent	Monovalent (Omicron BA.5) vs Bivalent (Original and Omicron BA.5)
GMTR[1]	0.9	1.0	0.9
95% CI	0.78, 1.08	0.84, 1.20	0.77, 1.09
Difference in SRRs[2], %	-0.4	0.6	-1.0
95% CI	-8.1, 7.2	-7.2, 8.3	-8.7, 6.6

Source: Table 14.2.1.2.1 in the "14.2 Efficacy Data Summary Figures and Tables"
Abbreviations: CI=confidence interval, GMT=geometric mean titer, ID_{50}=50% inh bitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
1. 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.
2. 95% CI for the percentage difference in SRRs is calculated based on the method of Miettinen and Nurminen.

Table 5 shows that on Day 28 post-vaccination against the ancestral (Wuhan) pseudovirus:

- The estimated GMTR of the monovalent vaccine (Omicron BA.5) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) pseudovirus was 0.9 with 95% confidence intervals: 0.78, 1.08 (the lower limit of the 95% CI around the GMTR is >0.67).
- The estimated percentage difference in SRRs of the monovalent vaccine (Omicron BA.5) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) pseudovirus was -0.4% with 95% confidence intervals: -8.1%, 7.2% (the lower limit of the 95% CI around the percentage difference in SRRs is >-10%).

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 currently circulating subvariant. The monovalent vaccine (Omicron BA.5) induced the following 50% neutralizing antibody responses against the Omicron XBB.1.5 pseudovirus displayed in Table 6.

Table 6. Summary of Serum Neutralizing Antibody Titers Against the Omicron XBB.1.5 Pseudovirus Following Initial Vaccination, Per-Protocol Immunology Subset

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

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
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[1]	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% inh bitory dilution, GMFR=geometric mean fold rise, GMTR=ratio of GMT between groups, SRR=seroresponse rate.
N=number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set.
n1=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set within each visit with non-missing data.
n2=Number of subjects in the assay-specific Per-Protocol Immunogenicity Analysis Set with non-missing data at both Day 0 and Day 28.
n3=Number of subjects achieving seroresponse.
1. 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.

Table 7. Comparison of Serum Neutralizing Antibody Titers Against the Omicron XBB.1.5 Pseudovirus Following Initial Vaccination, Per-Protocol Immunology Subset

Comparison Between Groups	Monovalent (Omicron BA.5) vs Original Monovalent	Bivalent (Original and Omicron BA.5) vs Original Monovalent	Monovalent (Omicron BA.5) vs Bivalent (Original and Omicron BA.5)
GMTR[1]	2.6	1.9	1.4
95% CI	2.23, 3.15	1.62, 2.23	1.16, 1.68
Difference in SRRs[2], %	32.4	18.5	13.9
95% CI	25.2, 39.4	12.0, 25.2	5.4, 22.2

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% inh bitory dilution; GMTR=ratio of GMT between groups; SRR=seroresponse rate.
1. 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.
2. 95% CI for the percentage difference in SRRs is calculated based on the method of Miettinen and Nurminen

As shown in Table 7, the monovalent vaccine (Omicron BA.5) induced superior GMTs (GMTR 2.6 with 95% CIs 2.23,3.15) and noninferior SRRs (percentage difference in SRRs of 32.4% with 95% CI: 25.2, 39.4) against the Omicron XBB.1.5 sublineage as compared to those of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) on Day 28 post-vaccination,

thus demonstrating a level of vaccine cross-reactivity against a circulating Omicron XBB-lineage virus.

6.2.1.4 Safety Results: Study 311 Part 2

Study 311 Part 2 safety data included solicited local AEs, solicited systemic AEs, unsolicited AEs, treatment-related unsolicited AEs, and a median of 70 days of safety follow up for MAAEs, SAEs, and AESIs.

Table 8 presents an overall summary of solicited and unsolicited AEs.

Table 8. Overall Solicited and Unsolicited Adverse Events Following Initial Booster Vaccination With Monovalent (Omicron BA.5), Original Monovalent, or Bivalent (Original and Omicron BA.5) in Adult Participants Who Previously Received ≥3 Vaccinations with COVID-19 mRNA Vaccines, Safety Analysis Set

Parameter	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	187 (74.2)	196 (78.1)	204 (78.8)
Grade 3 or higher	7 (2.8)	12 (4.8)	10 (3.9)
Solicited local AEs	153 (60.7)	168 (66.9)	169 (65.3)
Grade 3 or higher	4 (1.6)	2 (0.8)	2 (0.8)
Solicited systemic AEs	142 (56.3)	139 (55.4)	155 (59.8)
Grade 3 or higher	5 (2.0)	10 (4.0)	10 (3.9)
Unsolicited AEs through 36 days after vaccination	--	--	--
Any unsolicited AE	54 (21.3)	64 (25.5)	58 (22.4)
Treatment-related	3 (1.2)	5 (2.0)	8 (3.1)
Severe	1 (0.4)	0	3 (1.2)
Treatment-related	0	0	1 (0.4)
Unsolicited AEs through data cutoff date	--	--	--
Any SAE	4 (1.6)	1 (0.4)	1 (0.4)
Treatment-related	1 (0.4)	0	0
Any unsolicited AE leading to vaccination discontinuation	1 (0.4)	0	0
Treatment-related	1 (0.4)	0	0
Any MAAE	24 (9.4)	32 (12.7)	21 (8.1)
Treatment-related	0	0	2 (0.8)
Severe MAAE	0	0	1 (0.4)
Treatment-related	0	0	0
Any AESI: PIMMC[1]	1 (0.4)	0	1 (0.4)
Treatment-related	1 (0.4)	0	1 (0.4)

Parameter	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 (%)
Any AESI: PIMMC[2]	0	0	0
Any AESI: PIMMC[3]	1 (0.4)	0	1 (0.4)
Treatment-related	1 (0.4)	0	1 (0.4)
Any AESI: complications due to COVID-19	1 (0.4)	0	0
Any myocarditis/pericarditis	0	0	0

Source: Adapted from Study 311 Part 2. Table 37, T14.3.1.1, and Table 14.3.2.1 submitted to EUA 28237/130.
Abbreviations: AE=adverse event; AESI=adverse events of special interest; CRF=case report form; MAAE=medically attended adverse event; mRNA=messenger ribonucleic acid; 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; SAE=serious adverse event; potential immune-mediated medical conditions.
*The numbers N for those who completed e-Diary for solicited reactions are 252 (Group F), 251 (Group G), and 259 (Group H). The %s for solicited AEs in the table are based on these Ns. Solicited local and systemic AEs were reported within 7 days (Days 0 to 6) after booster vaccination.
1. PIMMCs according to investigator reported in the CRF.
2. PIMMCs according to protocol-defined criteria.
3. PIMMCs according to protocol-defined criteria or the investigator reported in the CRF.
Note: If any solicited AE extended beyond 6 days after vaccination (toxicity grade ≥1), it was recorded as an AE with the start date the 7th day following the relevant study vaccination and followed to resolution. The 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.
Note: Relationship and severity were based on the data reported by site – i.e., missing information was not imputed.
Note: Maximum toxicity grading for solicited AEs is standardized according to the FDA toxicity grading scale: Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, and Grade 4=Potentially Life Threatening.

Solicited local (injection site) adverse reactions (ARs)

Table 9 summarizes the solicited local injection site ARs reported by severity.

Table 9. Solicited Local Injection Site Adverse Reactions for 7 Days Following Initial Booster Vaccination With Monovalent (Omicron BA.5), Original Monovalent, or Bivalent (Original and Omicron BA.5) in Participants Who Previously Received ≥3 Vaccinations with COVID-19 mRNA Vaccines, Safety Analysis Set

Parameter	Group F Monovalent (Omicron BA.5) N=252 n (%)	Group G Original Monovalent N=251 n (%)	Group H Bivalent (Original and Omicron BA.5) N=259 n (%)
Any local injection site AR	--	--	--
Any Grade	153 (60.7)	168 (66.9)	169 (65.3)
Grade 3	4 (1.6)	2 (0.8)	2 (0.8)
Grade 4	0	0	0
Pain/Tenderness	--	--	--
Any Grade	153 (60.7)	166 (66.1)	169 (65.3)
Grade 3	4 (1.6)	2 (0.8)	2 (0.8)
Grade 4	0	0	0
Pain	--	--	--
Any grade	83 (32.9)	98 (39.0)	98 (37.8)
Grade 3	3 (1.2)	0	2 (0.8)
Grade 4	0	0	0

Parameter	Group F Monovalent (Omicron BA.5) N=252 n (%)	Group G Original Monovalent N=251 n (%)	Group H Bivalent (Original and Omicron BA.5) N=259 n (%)
Tenderness	--	--	--
Any grade	140 (55.6)	149 (59.4)	153 (59.1)
Grade 3	1 (0.4)	2 (0.8)	1 (0.4)
Grade 4	0	0	0
Redness	--	--	--
Any grade	5 (2.0)	8 (3.2)	6 (2.3)
Grade 3	0	0	0
Grade 4	0	0	0
Swelling	--	--	--
Any grade	8 (3.2)	6 (2.4)	6 (2.3)
Grade 3	0	0	0
Grade 4	0	0	0

Source: from T14.3.2.1
Abbreviations: AR=adverse reaction; FDA=United States Food and Drug Administration; mRNA=messenger ribonucleic acid; N=number of participants in the Safety Analysis Set within each treatment arm who received the booster dose and completed at least 1 day of the post- booster dose reactogenicity diary; n=number of participants who reported at least 1 AR
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

As shown in Table 9, frequencies of local injection site ARs were relatively balanced across the 3 vaccine groups, occurring with incidence rates 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. Pain and 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).

Solicited systemic ARs
Table 10 presents a summary of solicited systemic ARs by severity.

Table 10. Solicited Systemic Adverse Reactions for 7 Days Following Initial Booster Vaccination With Monovalent (Omicron BA.5), Original Monovalent, or Bivalent (Original and Omicron BA.5) in Participants Who Previously Received ≥3 Vaccinations With COVID-19 mRNA Vaccines, Safety Analysis Set

Parameter	Group F Monovalent (Omicron BA.5) N=252 n (%)	Group G Original Monovalent N=251 n (%)	Group H Bivalent (Original and Omicron BA.5) N=259 n (%)
Any systemic AR	--	--	--
Any Grade	142 (56.3)	139 (55.4)	155 (59.8)
Grade 3	5 (2.0)	10 (4.0)	10 (3.9)
Grade 4	0	0	0
Fatigue/malaise	--	--	--
Any Grade	106 (42.1)	103 (41.0)	97 (37.5)
Grade 3	3 (1.2)	7 (2.8)	8 (3.1)
Grade 4	0	0	0
Fatigue	--	--	--
Any Grade	97 (38.5)	94 (37.5)	88 (34.0)
Grade 3	2 (0.8)	7 (2.8)	8 (3.1)
Grade 4	0	0	0
Malaise	--	--	--
Any Grade	48 (19.0)	42 (16.7)	36 (13.9)
Grade 3	3 (1.2)	3 (1.2)	4 (1.5)
Grade 4	0	0	0
Muscle pain	--	--	--
Any Grade	59 (23.4)	71 (28.3)	67 (25.9)
Grade 3	1 (0.4)	2 (0.8)	2 (0.8)
Grade 4	0	0	0
Nausea/vomiting	--	--	--
Any Grade	19 (7.5)	18 (7.2)	19 (7.3)
Grade 3	1 (0.4)	0	0
Grade 4	0	0	0
Joint pain	--	--	--
Any Grade	18 (7.1)	20 (8.0)	19 (7.3)
Grade 3	0	1 (0.4)	1 (0.4)
Grade 4	0	0	0
Headache	--	--	--
Any Grade	73 (29.0)	73 (29.1)	74 (28.6)
Grade 3	4 (1.6)	2 (0.8)	3 (1.2)
Grade 4	0	0	0
Fever	--	--	--
Any Grade	2 (0.8)	2 (0.8)	4 (1.5)
Grade 3	0	0	1 (0.4)
Grade 4	0	0	0

Source: T14.3.2.1
Abbreviations: AR=adverse reaction
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:

As shown in Table 10, the proportions 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). Grade 3 or higher solicited systemic ARs were reported by 2.0%, 4.0%, and 3.9% of participants 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. No solicited systemic grade 4 ARs were reported in any vaccine group.

Unsolicited AEs

Unsolicited non-serious AEs (collected through 36 days post-vaccination) were reported by 21.3%, 25.5%, and 22.0% of participants in the in the monovalent vaccine (Omicron BA.5), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and bivalent vaccine (Original and Omicron BA.5) groups, respectively.

Unsolicited AEs were most frequently reported 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. Overall, the frequencies of individual unsolicited AEs were balanced across the 3 vaccine groups.

Severe unsolicited AEs were reported by 1 participant (0.4%) in the Novavax COVID-19 Vaccine, Adjuvanted (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. The severe unsolicited AE of diarrhea was considered treatment related.

Treatment-related unsolicited AEs were reported by 1.2%, 2.0%, and 3.1% 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 unsolicited treatment-related 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 unsolicited treatment-related AEs 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 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.

AEs Leading to Vaccine or Study Discontinuation

One (0.4%) participant experienced an unsolicited AE leading to study vaccine discontinuation. This AE was considered treatment-related and involved IVth cranial nerve paralysis (see SAE narrative below).

No unsolicited AEs led to study discontinuation.

SAEs

SAEs were defined as an event that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. SAEs were reported by 1.6%, 0.4%, and 0.8% 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. Table 11 presents a summary of SAEs.

Table 11. Serious Adverse Events Following Initial Booster Vaccination With Monovalent (Omicron BA.5), Original Monovalent, or Bivalent (Original and Omicron BA.5) in Participants Who Previously Received ≥3 Vaccinations with COVID-19 mRNA Vaccines, Safety Analysis Set

Preferred Term	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 (%)
Any SAE	4 (1.6)	1 (0.4)	2 (0.8)
Acute coronary syndrome	1 (0.4)	0	0
Acute myocardial infarction	1 (0.4)	0	0
Limb injury	0	0	1 (0.4)
Overdose	0	1 (0.4)	0
Non-cardiac chest pain	1 (0.4)	0	0
IVth nerve paralysis	1 (0.4%)	0	0
VIth nerve paralysis	0	0	1 (0.4)

Source: T14.3.6.1.5

Abbreviations: AE=adverse event; E=number of events experienced; MedDRA=Medical Dictionary for Regulatory Activities; mRNA=messenger r bonucleic acid; N=number of participants in the Safety Analysis Set within each treatment; n=unique number of participants experiencing the AE; SAE=serious adverse event.

A total of 7 SAEs were reported by 7 participants: 4 (1.6%) in the monovalent vaccine (Omicron BA.5) group, 1 (0.4%) in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 2 (0.8%) in the bivalent vaccine (Original and Omicron BA.5) group. Of these SAEs, the events of IVth and VIth 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 post-vaccination. Approximately 7 days post-vaccination, she experienced both headache and double vision. A head computerized tomography (CT) was performed 9 days post-vaccination 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 post-vaccination with superior oblique IVth cranial nerve palsy. No medical treatment was given, and as of 56 days post-vaccination, the symptoms

were ongoing but slowly improving. A brain and orbit MRI with gadolinium performed 132 days post-vaccination was notable for symmetrical superior oblique muscle bilaterally with normal enhancement and no evidence of superior oblique inflammation. At that time, the participant reported pain and diplopia when fatigued and the event was considered resolving. The Principal Investigator assessed the IVth cranial nerve palsy as moderate in intensity and related to the study vaccine. The Sponsor 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 and the available information is insufficient to conclusively determine a causal relationship with the vaccine, 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 nerve palsy (originally classified by the sponsor 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, cerebrovascular accident, and diplopia in 2020 that self-resolved. The participant experienced the onset of blurriness/ double vision approximately 14 days post-vaccination 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 post-vaccination. 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 Sponsor 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: Underlying type 1 diabetes can lead to microvascular disease, which is a plausible etiology of cranial nerve VI paralysis and a potential alternate explanation or risk factor for the participant's symptoms. The fact that this patient also had a pre-existing residual right eye cranial nerve palsy, likely from a microvascular cause, increases the likelihood that the emergence of a new cranial nerve palsy in the left eye is also related to underlying microvascular disease. However, considering the temporal association between vaccination and the onset of symptoms within 14 days as well as the biologic plausibility for a potential autoimmune mechanism, this reviewer considers this case of VIth cranial nerve paralysis to be possibly related to the study vaccine.

Novavax conducted a search of their clinical trial safety database (which included studies 2019nCoV-101 parts 1 and 2, 2019nCoV-301 adult, 2019nCoV-501, 2019nCoV-302, and 2019nCoV-311 part 2) for any other cases of eye movement disorders involving cranial nerve paralysis occurring up to 42 days post-vaccination. The search yielded no additional cases. CBER also requested an observed-to-expected analysis of cranial nerve paralysis/ palsies involving eye movement disorders. The background rate of cranial nerve paralysis affecting eye

movements (composite of IVth and VIth cranial nerve palsy) is 17.03 cases per 100,000 person-years,[37,38] corresponding to an expected 1.26 cases in a 42-day window. With the 2 cases reported in Study 311 Part 2, the observed-to-expected ratio was 1.59 (95% confidence intervals: 0.19, 5.7), which is comparable to the background rate.

Although there are plausible potential alternative etiologies or contributing factors for these oculomotor cranial nerve palsy events, such as underlying type 1 diabetes-related microvascular disease[38] or an underlying congenital anomaly presenting late in adulthood,[37] the clustering of the cases, the temporal relationship, and the biologic plausibility for a vaccine induced immune-mediated mechanism[39] support that these cases are at least possibly related to the study vaccine. In addition to inclusion of these events in product labeling (see Fact Sheet), this potential safety signal will be addressed via enhanced pharmacovigilance in postmarketing (see Section 7.5 for details).

Other SAEs

The remaining SAEs were not considered related to vaccine by the investigator and Sponsor, and this reviewer agrees with these assessments based on lack of temporal association, biological implausibility, and/or alternative etiology. Brief details of each SAE are provided below.

- A 51-year-old White female, in the monovalent vaccine (Omicron BA.5) group, with a history of anxiety, depression, and panic disorder experienced an SAE of musculoskeletal (non-cardiac) chest pain 43 days after vaccination. She was found to have a positive COVID-19 test and her cardiac enzymes and electrocardiogram did not reveal a cardiac etiology of her symptoms. She was treated with oral aspirin, and symptoms improved but did not resolve through the course of study follow-up.
- A 64-year-old White male, in the monovalent vaccine (Omicron BA.5) group, with a history of hypertension, gout, bronchiectasis, nephrolithiasis, and dyslipidemia experienced an SAE of acute coronary syndrome 40 days post-vaccination. Coronary angiogram revealed 2-vessel coronary artery disease, and he underwent successful surgery for blockage with stent placement.
- A 64-year-old White male, in the monovalent vaccine (Omicron BA.5) group, with a history of hypertension, coronary artery bypass graft, ischemic heart disease, 2 prior non-ST elevation myocardial infarctions, type 2 diabetes, and diabetic nephropathy experienced an SAE of acute myocardial infarction approximately 32 days post-vaccination. He experienced the onset of nasal congestion and tested positive for COVID-19. He reported events of collapse, shortness of breath, hypoxia, and pleuritic chest pain. Cardiac workup revealed a non-ST elevation myocardial infarct with 3-vessel coronary artery disease and confirmed positive COVID-19 infection. He was treated and discharged from the hospital 7 days after admission.
- A 28-year-old White female, in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, with a history of borderline personality disorder, polycystic ovarian syndrome, migraines, adjustment disorder, and anaphylaxis to sumatriptan reported an SAE of intentional overdose of multiple substances approximately 40 days after vaccination. She was evaluated and treated in the Emergency Department with intravenous N-acetylcysteine and discharged the same day.
- A 42-year-old White male, in the bivalent vaccine (Original and Omicron BA.5) group, experienced an SAE of limb injury due to a router tool approximately 23 days post-vaccination.

- There were no deaths reported in the study.

Adverse events of special interest (AESIs)
Three participants experienced AESIs. A participant in the monovalent vaccine (Omicron BA.5) group experienced an SAE of acute myocardial infarction that was also categorized as an AESI as a complication due to COVID-19 (see narrative described above).

The remaining AESI cases included the cranial nerve palsies described in detail above, which were categorized as PIMMCs.

Subgroup Analyses
Subgroup analyses for solicited local injection site ARs conducted by age, sex, race, and ethnicity revealed the following findings:

Solicited local injection site ARs within the first 7 days post-vaccination were reported at higher frequencies by participants in the 18 years through 54 years of age subgroup (ranging from 65.1% to 69.9% across the 3 vaccine groups) than by participants 55 years of age (39.5% to 55.3%). Grade 3 solicited local ARs were reported by fewer than 2% of participants 18 years through 54 years of age and no participants 55 years of age and older. Subgroup analysis by sex revealed that female participants reported a higher frequency and severity of solicited local injection site ARs (72.1% to 73.4%) than male participants (46.4% to 59.5%). Solicited local injection site ARs were balanced across the 3 vaccine groups for White participants (61.3% to 66.8%), however, 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.

Solicited systemic ARs were reported at higher frequencies by participants in the 18 years through 54 years of age subgroup (57.4% to 64.6%) within the first 7 days after vaccination compared to participants 55 years of age and older (34.9% to 45.2%). Grade 3 solicited local ARs were reported by fewer than 5% of participants in either age subgroup. Subgroup analysis by sex showed that female participants reported a higher frequency of solicited systemic ARs (60.0% to 64.7%) than male participants (49.1% to 54.2%) after vaccination. Solicited systemic ARs were balanced across the 3 vaccine groups for White participants (58.8% to 61.9%), however, 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 there were too few participants of other ethnicities.

Unsolicited AEs were reported at similar frequencies by participants in the 18 years through 54 years of age subgroup across the 3 vaccine groups. The 55 years of age and older subgroup reported higher rates of unsolicited AEs in the monovalent vaccine (Omicron BA.5) group (25.6 %) and Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group (31.0%) compared to the bivalent vaccine (Original and BA.5) group (19.1%). Subgroup analysis by sex revealed similar frequencies of unsolicited AEs between male participants (18.6% to 24.2%) and female participants (20.9% to 27.9%) across the 3 vaccine groups. Unsolicited AEs were balanced across the 3 vaccine groups for White participants (24.6 to 25.4%), however, 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 there were too few participants of other ethnicities.

MAAEs were reported at higher rates by participants in the 55 years of age and older group who received the monovalent (Omicron BA.5) vaccine (25.6%) and Novavax COVID-19 Vaccine,

Adjuvanted (Original monovalent) (31.0%) compared to those in the bivalent (Original and Omicron BA.5) vaccine group (19.1%). Reported rates of MAAEs were similar for the 18 years through 54 years of age group across the 3 vaccines (20.4% to 24.4%). When analyzed by sex, male participants (18.6% to 24.2%) and female participants (20.9% to 27.9%) reported similar rates of MAAEs across the 3 vaccine groups. MAAEs were balanced across the 3 vaccine groups for White participants (24.6% to 25.4%), however, 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 there were too few participants of other ethnicities.

Subgroup analyses of SAEs by age, sex, race, ethnicity, and by previous COVID-19 vaccine regimen were of limited value, as there were too few participants with serious events.

6.2.1.5 Summary of Findings: Study 311 Part 2

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older not previously vaccinated with a COVID-19 vaccine and the effectiveness of a single-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine is inferred from immunogenicity data from Study 311 Part 2 as follows:

- Based on a descriptive analysis, 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), it is reasonable to expect that in individuals 18 years of age and older that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).
- Additional supportive immunogenicity data includes: (1) descriptive 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, the virus upon which the currently authorized formulation was based, and (2) superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by the bivalent vaccine (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), supporting that it is reasonable to expect that multiple modified vaccines using a similar manufacturing process and the same antigen and adjuvant dose can elicit a superior neutralizing antibody response to an Omicron sublineage compared the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).
- Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age not previously vaccinated with a COVID-19 vaccine and the effectiveness of a single-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine is extrapolated from immunogenicity data from Study 311 Part 2 as follows:
- The superior neutralizing antibody responses (as measured by GMTR) and non-inferior SRRs induced by the monovalent vaccine (Omicron BA.5) and bivalent (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) can be extrapolated to adolescents in the context of previously reviewed

comparable efficacy and immunogenicity results between individuals 18 years of age and older and individuals 12 years through 17 years of age observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see the Decision Memorandum). Therefore, for individuals 12 years through 17 years of age, it is reasonable to expect that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

Data from Study 311 Part 2 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). The monovalent vaccine (Omicron BA.5), the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.5) were well tolerated with 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).[40,41] Two related SAEs of oculomotor cranial nerve palsy were reported in close temporal relationship to vaccination. In addition to inclusion of these events in product labeling (see Fact Sheet), 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)" as an Important Potential Risk in the pharmacovigilance plan and enhanced pharmacovigilance in postmarketing (see Section 7.5 for details). No other new safety concerns were identified.

6.2.2 Study 311 Part 1

The sections below summarize interim immunogenicity and safety data from ongoing Study 311 Part 1, in which participants who had been previously vaccinated with 3 doses of an mRNA COVID-19 vaccine (any combination of Pfizer-BioNTech and/or Moderna original monovalent and/or bivalent COVID-19 vaccines) 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 included a total of 5 µg of antigen and 50 µg of Matrix-M adjuvant. The interim analysis includes data collected through a median of 66 days in 831 participants 18 years through 64 years of age.

6.2.2.1 Study Design: Study 311 Part 1

Study 311 Part 1 was originally designed 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) 14 days after vaccination. This FDA immunogenicity review analyzes Day 14 pre-specified co-primary endpoints against the Omicron BA.1 sublineage and, for the purpose of standardizing our analysis of the immune response 1 month after vaccination in both Study 311 Parts 1 and 2, includes a similar descriptive analysis of both the monovalent (Omicron BA.1) and bivalent vaccine (Original and Omicron BA.1) endpoints at 28 days post-vaccination. The FDA immunogenicity review also includes descriptive review of Study 311 Part 1 secondary endpoints, which evaluated neutralizing antibody immune responses against the ancestral (Wuhan) sublineage. See additional details in the section below entitled "Immunogenicity Statistical Analysis Plan."

All enrolled participants 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 on Day 0:

- 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)

Immunogenicity Evaluation

Blood samples for immunogenicity assessments were collected and analyzed before vaccination on Day 0 and on Days 7, 14, and 28 post-vaccination. To characterize the immune response induced by each of the 3 study vaccines, blood samples were analyzed for Omicron BA.1 sublineage and ancestral (Wuhan) strain neutralizing antibody GMTs and 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.

Immunogenicity Population

Available immunogenicity data at the time of interim study analysis were from randomized participants who received a single dose of study vaccine through the data cut-off date of September 1, 2022. The PP Analysis Set included the subset of participants who had a negative test for prior SARS-CoV-2 infection (tested via both anti-N (nucleocapsid) and PCR at the beginning of the study prior to vaccination), received the study vaccine according to protocol, and completed the study blood tests (a total of 356 participants on Day 14 and 335 participants on Day 28). 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 a positive baseline anti-N result (n=698).

Immunogenicity Statistical Analysis Plan

Immune responses following a single dose of the monovalent vaccine (Omicron BA.1) and a single dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) were assessed using the following prespecified co-primary endpoints on Day 14 post-vaccination endpoints:

1. Neutralizing antibody GMTs against the BA.1 sublineage
2. SRRs against the BA.1 sublineage

The following endpoints were also analyzed:

- Neutralizing antibody GMTs against the ancestral (Wuhan) strain
- SRRs against the ancestral (Wuhan) strain

The above endpoints were used to make comparisons between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to evaluate the following:

- Superiority of the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for neutralizing antibody GMTs against the Omicron BA.1 sublineage. Criterion for superiority is met if the 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) by percentage difference of SRRs against the Omicron BA.1 sublineage. Criterion for non-inferiority 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 (monovalent vaccine [Omicron BA.1] minus Novavax COVID-19 Vaccine, Adjuvanted [Original monovalent]) is 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 ais met if the percentage difference in SRRs is greater than -10% (i.e., lower bound of the two-sided 95% CI >-10%)

Similar 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 28 compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

Safety Evaluation

Participants remained under observation for at least 30 minutes post-vaccination to be monitored for any immediate hypersensitivity and anaphylaxis reactions. Participants used an eDiary to record reactogenicity on the day of vaccination and for an additional 6 days after vaccination.

Unsolicited AEs were collected through Day 36 post-vaccination. Collection of treatment-related MAAEs, AESIs, and SAEs were planned to be collected through 8 months post-vaccination. Safety data through the data extraction date of September 1, 2022, were available for the interim study analysis, representing approximately 2 months of data collection post-vaccination.

AESIs included myocarditis/pericarditis, PIMMCs, and complications of COVID-19.

Safety Analysis Population

Available safety data in the interim study analysis was reported for all randomized participants who received 1 dose of study vaccine through the data cut-off date of September 1, 2022. Of the 831 randomized participants, 829 received a study vaccine, all of whom were included in the Safety Analysis Set (Table 15).

Safety Statistical Analysis Plan

AEs were categorized by frequency, maximum severity, seriousness, and relationship to study intervention using SOC and PT according to MedDRA.

6.2.2.2 Demographics and Disposition: Study 311 Part 1

Participant Disposition

Of the 835 participants enrolled, 831 were randomized to receive vaccination, and 6 (0.7%) had discontinued study participation as of the data cutoff date of September 01, 2022. These discontinuations included 2 (0.7%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 4 (1.4%) participants in the bivalent vaccine (Original and Omicron BA.1) group. The most common reason for discontinuation was participant decision to withdraw from the study. One participant assigned to the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group withdrew due to an adverse event involving acute psychosis, which was assessed to be unrelated to the study vaccine (see narrative for participant).

The full analysis set was comprised of 829 randomized participants who received at least 1 dose of study vaccine, regardless of protocol violations or missing data, including: 274 who received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), 286 who received monovalent vaccine (Omicron BA.1), and 269 who received bivalent vaccine (Original and Omicron BA.1).

Immunogenicity Population

The immunogenicity population on Day 14 post-vaccination included 356 (42.8% of those randomized) and on Day 28 post-vaccination included 335 participants (40.3% of those randomized). These participants, who comprised the PP Analysis Set on each respective study day, received the study vaccine, were negative at baseline for SARS-CoV-2 infection by PCR and anti-Nucleocapsid (anti-N) antibody testing, had no major protocol violations, and had serology results collected on in each of the 3 vaccine groups. A total of 473 (56.9%) participants were excluded from the Day 14 PP analysis set (494 [59.4%] from the Day 28 analysis set), with baseline positivity for SARS-CoV-2 infection based on an anti-N testing as the most frequent reason for exclusion (50.5%, 51.5%, and 49.6% excluded from Day 14 PP analysis set for positive anti-N test, respectively)

The PP2 Analysis Set contains all participants who were included in the PP Analysis Set with the addition of those who tested positive for SARS-CoV-2 infection based on an anti-N testing at baseline in the 3 vaccine groups: 241 (86.4%) in the monovalent vaccine (Omicron BA.1) group, 236 (86.1%) in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 221 (79.5%) in the bivalent vaccine (Original and Omicron BA.1) group. Both the PP Analysis set and PP2 Analysis sets excluded individuals with active COVID-19 infection or positive PCR testing at baseline.

Our review focuses on the PP2 immunogenicity population, as it is likely to be more representative of the heterogeneity of the indicated population than the PP Analysis Set, which excluded participants who tested positive for SARS-CoV-2 infection based on an anti-N test at baseline.

Safety Population

The safety population was comprised of 829 participants (99.8% of those randomized). No participants were excluded from the safety population. The median duration of safety follow-up time after study vaccination was approximately 2 months (66 days).

Table 12 presents the participant demographics and baseline disease characteristics in the Safety Analysis Set.

Table 12. Participant Demographics and Baseline Disease Characteristics, Safety Analysis Set

Parameter	Group C Monovalent (Omicron BA.1) N=286	Group D Original Monovalent N=274	Group E Bivalent (Original and BA.1) N=269
Age (years)	--	--	--
Mean (SD)	40.4 (12.14)	40.1 (11.51)	39.9 (12.35)
Median	42.0	41.0	41.0
Minimum-maximum	18-64	18-64	18-64
Sex, n (%)	--	--	--
Male	133 (46.5)	131 (47.8)	118 (43.9)
Female	153 (53.5)	143 (52.2)	151 (56.1)
Race, n (%)	--	--	--
White	233 (81.5)	215 (78.5)	220 (81.8)
Black or African American	0	2 (0.7)	0
Aboriginal Australian	2 (0.7)	1 (0.4)	2 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	1 (0.4)
Asian	37 (12.9)	45 (16.4)	39 (14.5)
Mixed origin	5 (1.7)	3 (1.1)	1 (0.4)
Other	8 (2.8)	8 (2.9)	6 (2.2)
Not reported	0	0	0
Ethnicity, n (%)	--	--	--
Australian	252 (88.1)	236 (86.1)	233 (86.6)
Aboriginal/Torres Strait Islanders	4 (1.4)	3 (1.1)	2 (0.7)
Hispanic or Latino	6 (2.1)	8 (2.9)	6 (2.2)
Not reported	12 (4.2)	15 (5.5)	17 (6.3)
Unknown	10 (3.5)	11 (4.0)	9 (3.3)
Missing	2 (0.7)	1 (0.4)	2 (0.7)
BMI (kg/m^2)	--	--	--
n	284	270	267
Mean (SD)	28.07 (6.436)	28.01 (5.321)	27.40 (5.686)
Median	26.90	27.50	26.30
Minimum-maximum	18.1-55.8	17.4-47.2	17.7-50.1
BMI (kg/m^2) category, n (%)	--	--	--
Underweight (<18.0)	0	3 (1.1)	2 (0.7)
Normal (18.0-24.9)	106 (37.1)	75 (27.4)	104 (38.7)
Overweight (25.0-29.9)	87 (30.4)	108 (39.4)	90 (33.5)
Obese (≥30.0)	91 (31.8)	84 (30.7)	71 (26.4)
Missing	2 (0.7)	4 (1.5)	2 (0.7)

Parameter	Group C Monovalent (Omicron BA.1) N=286	Group D Original Monovalent N=274	Group E Bivalent (Original and BA.1) N=269
Regimen of previous COVID-19 vaccine, n (%)	--	--	--
Moderna	0	2 (0.7)	5 (1.9)
Pfizer-BioNTech	213 (74.5)	214 (78.1)	200 (74.3)
Mixed	73 (25.5)	58 (21.2)	64 (23.8)
Moderna-Moderna-Pfizer	1 (0.3)	1 (0.4)	0
Moderna-Pfizer-Pfizer	2 (0.7)	0	1 (0.4)
Moderna-Pfizer-Moderna	0	0	0
Pfizer-Pfizer-Moderna	70 (24.5)	56 (20.4)	63 (23.4)
Pfizer-Moderna-Moderna	0	1 (0.4)	0
Pfizer-Moderna-Pfizer	0	0	0
Previous COVID-19, n (%)	--	--	--
Yes	18 (6.3)	19 (6.9)	17 (6.3)
No	268 (93.7)	255 (93.1)	252 (93.7)
Qualitative anti-N, n (%)	--	--	--
Positive	145 (50.7)	141 (51.5)	134 (49.8)
Negative	141 (49.3)	133 (48.5)	135 (50.2)
PCR, n (%)	--	--	--
Positive	11 (3.8)	12 (4.4)	14 (5.2)
Negative	275 (96.2)	262 (95.6)	255 (94.8)
Anti-N / PCR, n (%)[1]	--	--	--
Positive	149 (52.1)	145 (52.9)	137 (50.9)
Negative	137 (47.9)	129 (47.1)	132 (49.1)
Time between last previous COVID-19 vaccine and booster dose of study vaccine (days)	--	--	--
Mean (SD)	178.2 (38.49)	182.4 (36.35)	178.7 (36.57)
Median	177.0	182.0	180.0
Minimum-maximum	84-440	91-329	77-313

Parameter	Group C Monovalent (Omicron BA.1) N=286	Group D Original Monovalent N=274	Group E Bivalent (Original and BA.1) N=269
Interval between last previous COVID-19 vaccine and booster dose of study vaccine, n (%)	--	--	--
<90 days	1 (0.3)	0	1 (0.4)
90-120 days	15 (5.2)	15 (5.5)	18 (6.7)
>120-days	43 (15.0)	35 (12.8)	36 (13.4)
>150-180 days	98 (34.3)	81 (29.6)	81 (30.1)
>180-210 days	87 (30.4)	97 (35.4)	94 (34.9)
>210-240 days	26 (9.1)	32 (11.7)	25 (9.3)
>240-270 days	10 (3.5)	9 (3.3)	11 (4.1)
>270-300 days	4 (1.4)	2 (0.7)	1 (0.4)
>300-330 days	1 (0.3)	3 (1.1)	2 (0.7)
>330-360 days	0	0	0
>360 days	1 (0.3)	0	0

Source: Study 311 Part 1 Interim Study Report, Table 9, p. 36
Abbreviations: anti-N=anti-nucleocapsid protein; NVX-CoV2515=5 µg SARS-CoV-2 rS Omicron BA.1 sublineage with 50 µg Matrix-M adjuvant; NVX-CoV2373=5 µg SARS-CoV-2 rS prototype Wuhan strain with 50 µg Matrix-M adjuvant; NVX-CoV2373 + NVX-CoV2515=5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant (total); SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; PCR=polymerase chain reaction; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant sp ke protein nanoparticle vaccine; SD=standard deviation

Demographic characteristics were balanced across the 3 vaccine groups in the safety analysis set. Across groups, the median age was 41.0 to 42.0 years (range of 18 to 64 years in each group). The majority of participants in each group were female (52.2% to 56.1%), White (78.5% to 81.8%), and of Australian ethnicity (86.1% to 88.1%).

The median time between the most recent mRNA COVID-19 vaccine and the dose of study vaccine was approximately 6 months (177 to 182 days).

6.2.2.3 Immunogenicity Results: Study 311 Part 1

Table 13 and Table 14 present the pre-specified co-primary endpoints and success criteria for 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) for the PP Analysis Set on Day 14 post-vaccination.

Table 13. Summary of Geometric Mean Titers of Monovalent (Omicron BA.1) Against the Omicron BA.1 Virus at 14 Days After a Booster Dose Versus the Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) at 14 Days After a Booster Dose, Participants 18 Years through 64 Years of Age, PP Analysis Set[1]

Monovalent (Omicron BA.1) N=124[2] GMT (95% CI)[3]	Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) N=116[2] GMT (95% CI)[3]	GMT Ratio[4] [Monovalent (Omicron BA.1)/ Original monovalent] (95% CI)[4]	Met Success Criterion
130.8 (109.2, 156.7)	83.9 (69.6, 101.2)	1.6 (1.33, 2.03)	Yes[5]

Source: Adapted from Study 311 Part 1 Interim Study Report, Table 12, p. 46
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMT=geometric mean titer; MN50=microneutralization

assay with an inhibitory concentration of 50%; PP=Per-Protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
1. PP Analysis Set included participants who received study vaccine according to protocol, did not have serologic or virologic evidence of SARS-CoV-2 infection on or before the booster dose, and had no major protocol violations that were considered clinically relevant to impact immunogenicity.
2. The analysis included participants of the PP analysis set who had immunogenicity data available at baseline and at 14 days post booster dose.
3. The 95% CI for GMT were calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
4. An ANCOVA with vaccine group as fixed effect and baseline value as covariate was performed to estimate the GMT ratio. The mean difference between vaccine groups and the corresponding CI limits was then exponentiated to obtain the ratio of MN50 GMTs and the corresponding 95% CIs.
5. Success criterion is met if the lower bound of the two-sided 95% CI was above unity (i.e., >1).

Table 14. Summary of Seroresponse Rate of Monovalent (Omicron BA.1) Against the Omicron BA.1 Virus at 14 Days After a Booster Dose Versus the Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent) at 14 Days After a Booster Dose, Participants 18 Years through 64 Years of Age, PP Analysis Set[1]

Monovalent (Omicron BA.1) N=124[2] SRR[3] % (95% CI)[4]	Original Monovalent N=116[2] SRR[3] % (95% CI)[4]	Difference in SRR [Monovalent (Omicron BA.1) - Original Monovalent] % (95% CI)[5]	Met Success Criterion
73.4 (64.7, 80.9)	50.9 (41.4, 60.3)	22.5 (10.3, 34.2)	Yes[6]

Source: Adapted from Study 311 Part 1 Interim Study Report, Table 12, p. 46
Abbreviations: CI=confidence interval; MN_{50}=microneutralization assay with an inhibitory concentration of 50%; PP=Per-Protocol; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SRR=seroresponse rate.
1. PP Analysis Set included participants who received study vaccine according to protocol, did not have serologic or virologic evidence of SARS-CoV-2 infection on or before the booster dose, and had no major protocol violations that were considered clinically relevant to impact immunogenicity.
2. The analysis included participants of the PP analysis set who had immunogenicity data available at baseline and at 14 days post booster dose.
3. The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥ 4-fold rise in MN_{50} level.
4. The 95% CI for SRR was calculated using the exact Clopper-Pearson method.
5. The 95% CI for the difference in SRR was calculated based on the method of Miettinen and Nurminen.
6. Success criterion is met if the lower bound of the two-sided 95% CI was above -5%.

Immunogenicity results for the monovalent vaccine (Omicron BA.1) against the Omicron BA.1 sublineage based on pre-specified co-primary endpoints and success criteria for PP Analysis Set on Day 14 post-vaccination were as follows:

- 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% with 95% CIs: 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%).

These above immunogenicity results for the monovalent vaccine (Omicron BA.1), based on prespecified endpoints, meet success criteria. These analyses were limited by the fact that subjects who tested COVID-19 positive by serology testing were excluded, and results may not be generalizable to the overall population. Additional supportive descriptive analyses that are more generalizable are presented below.

Table 15 presents the PP2 Analysis Subset 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) 14 and 28 days after study vaccination.

Table 15. Summary 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

Parameter	Group C Monovalent (Omicron BA.1)	Group D Original Monovalent	Group E Bivalent (Original and BA.1)
Day 0 (baseline)[1]	--	--	--
n1	255	250	236
Median	160.0	160.0	160.0
Minimum-maximum	10-2560	10-2560	10-10240
GMT (MN_{50})	97.3	105.9	106.1
95% CI[2]	79.6, 118.9	86.4, 129.7	85.8, 131.1
Day 14	---	---	---
n1	247	244	232
Median	320.0	320.0	320.0
Minimum-maximum	10-5120	10-2560	10-5120
GMT (MN_{50})	318.2	218.1	252.7
95% CI[2]	269.8, 375.3	186.0, 255.7	213.1, 299.7
n2	247	244	232
GMFR referencing Day 0	3.3	2.1	2.4
95% CI[2]	2.9, 3.7	1.8, 2.3	2.1, 2.7
SRR ≥4-fold increase,3 n3/n2 (%)	134/247 (54.3)	78/244 (32.0)	95/232 (40.9)
Day 28	--	--	--
n1	238	234	215
Median	320.0	160.0	160.0
Minimum-maximum	10-5120	10-2560	10-10240
GMT (MN_{50})	284.8	195.7	218.7
95% CI[2]	241.8, 335.4	165.7, 231.2	183.1, 261.3
n2	238	234	215
GMFR referencing Day 0	2.9	1.9	2.0
95% CI[2]	2.5, 3.3	1.6, 2.2	1.8, 2.2
Percentage SRR ≥4-fold increase[3] % (n3/n2)	52.5% (125/238)	27.8% (65/234)	33.5% (72/215)
95% CI[4]	46.0, 59.0	22.1, 34.0	27.2, 40.2

Source: T14.2.1.1.3

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups; max=maximum; min=minimum; MN_{50}=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.

[1]Baseline was defined as the last non-missing assessment prior to booster vaccination.

[2]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.

[3]The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥4-fold rise in MN_{50} level.

[4]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 16. 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

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[1]	1.5	1.2	0.7
95% CI[1]	1.36, 1.77	1.02, 1.31	0.65, 0.85
Difference in SRR[2], %	22.3	9.0	-13.3
95% CI[6]	13.6, 30.6	0.3, 17.5	-22.0, -4.4
Day 28	--	--	--
GMTR[1]	1.5	1.1	0.7
95% CI[1]	1.29, 1.73	0.94, 1.25	0.63, 0.83
Difference in SRRs[2], %	24.7	5.7	-19.0
95% CI[2]	16.0, 33.1	-2.8, 14.2	-27.8, -9.9

Source: T14.2.1.1.3
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; GMFR=geometric mean fold rise; GMT=geometric mean titer; GMTR=ratio of GMT between groups; max=maximum; min=minimum; MN_{50}=microneutralization assay at an inhibitory concentration of 50%; N=number of participants in the assay-specific PP-IMM Analysis Subset 2; n1=number of participants in the assay-specific PP-IMM Analysis Set within each visit with non-missing data; n2=number of participants in the assay-specific PP-IMM 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; PP-IMM=Per-Protocol Immunogenicity; SRR=seroresponse rate.
1. 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.
2. 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

Table 16 shows the following results for the PP2 Analysis Set on Day 14 post-vaccination against the Omicron BA.1 virus:

Monovalent Vaccine (Omicron BA.1) Analysis

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.5 with 95% confidence intervals: 1.36, 1.77 (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 22.3% with 95% CIs: 13.6%, 30.6% (the lower limit of the 95% CI around the percentage difference in SRRs is >-5%).

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the Novavax COVID-19 Bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.2 with 95% confidence intervals: 1.02, 1.31 (the lower limit of the 95% CI around the GMTR >1).
- 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 9.0% with 95% CIs: 0.3%, 17.5% (the lower limit of the 95% CI around the difference in SRRs is >-5%).

The above analyses were described on Day 14 after vaccination, as this timepoint was

prespecified in the study protocol.

The following descriptive analyses on Day 28 after vaccination against the Omicron BA.1 virus provide a longer period of time to assess the magnitude of immune responses:

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.5 with 95% confidence intervals: 1.29, 1.73 (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 24.7% with 95% CIs: 16.0%, 33.1% (the lower limit of the 95% CI around the difference in SRRs is >-5%)

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the Novavax COVID-19 bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.1 with 95% confidence intervals: 0.94, 1.25 (the lower limit of the 95% CI around the GMTR >1).
- 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 5.7 with 95% CIs: -2.8%, 14.2% (the lower limit of the 95% CI around the difference in SRRs is >-5%).

Table 17 summarizes the immunogenicity results for the monovalent vaccine (Omicron BA.1), the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and for the bivalent Vaccine (Original and Omicron BA.1) against the ancestral (Wuhan) pseudovirus on Day 28 in the PP2 Analysis Set.

Table 17. Summary 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

Parameter	Group C Monovalent (Omicron BA.1) N=255	Group D Original Monovalent N=250	Group E Bivalent (Original and Omicron BA.1) N=236
Day 0 (baseline)[1]	--	--	--
n1	255	250	236
Median	1280.0	1280.0	1280.0
Minimum-maximum	20-40960	20-40960	40-81920
GMT (MN_{50})	1151.3	1280.0	1232.0
95% CI[2]	973.6, 1361.4	1078.1, 1519.7	1026.0, 1479.5

Parameter	Group C Monovalent (Omicron BA.1) N=255	Group D Original Monovalent N=250	Group E Bivalent (Original and Omicron BA.1) N=236
Day 14	--	--	--
n1	247	244	232
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[2]	1910.0, 2548.4	2347.9, 3109.4	2194.5, 2950.9
n2	247	244	232
GMFR referencing Day 0	1.9	2.1	2.1
95% CI[2]	1.8, 2.1	1.9, 2.4	1.9, 2.3
SRR ≥4-fold increase,[3] (%) (n3/n2)	32.0% (79/247)	32.8% (80/244)	35.8% (83/232)
95% CI[4]	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[2]	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[2]	1.5, 1.8	1.7, 2.2	1.5, 1.9
SRR ≥4-fold increase,[3] %, (n3/n2)	23.5% (56/238)	29.1% (68/234)	27.4% (59/215)
95% CI[4]	18.3, 29.4	23.3, 35.3	21.6, 33.9

Source: Study 311 Part 1 Interim Study Report, Table 17, p. 71
Abbreviations: CI=confidence interval; GMTR=geometric mean titer ratio; SRR=seroresponse rate
N=number of subjects in the assay-specific Analysis Set.
N1=Number of subjects in the assay-specific Analysis Set within each visit with non-missing data.
N2=Number of subjects in the assay-specific Analysis Set with non-missing data at both Day 0 and Day 28.
N3=Number of subjects achieving seroresponse.
1. Baseline was defined as the last non-missing assessment prior to booster vaccination.
2. The 95% CI for GMT and GMFR were calculated based on the t-distr bution of the log-transformed values then back transformed to the original scale for presentation.
3. The SRR was defined as percentage of participants at each post vaccination visit with a titer ≥4-fold rise in MN_{50} level.
4. The 95% CI for the percentage difference in SRRs was calculated using the exact Clopper-Pearson method.

Table 18. 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

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[1]	0.9	1.0	1.1
95% CI[1]	0.78, 0.99	0.85, 1.10	0.97, 1.25
Difference in SRRs[2], %	-0.8	3.0	3.8
95% CI[2]	-9.1, 7.5	-5.5, 11.5	-4.7, 12.3

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 28	--	--	--
GMTR[1]	0.8	0.9	1.1
95% CI[1]	0.72, 0.93	0.77, 1.00	0.94, 1.22
Difference in SRRs[2], %	-5.5	-1.6	3.9
95% CI[2]	-13.5, 2.4	-9.9, 6.8	-4.1, 12.0

Source: Study 311 Part 1 Interim Study Report, Table 17, p. 71
Abbreviations: CI=confidence interval; GMTR=geometric mean titer ratio; SRR=seroresponse rate
1. 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.
2. 95% CI for the percentage difference in SRR was calculated based on the method of Miettinen and Nurminen.

As shown in Table 18, the descriptive results on Day 14 after vaccination against the ancestral (Wuhan) strain were the following for the PP2 Analysis Set:

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 0.9 with 95% confidence intervals: 0.78, 0.99 criterion (the lower limit of the 95% CI around the GMTR was >0.67).

- The estimated percentage difference in SRRs of the monovalent vaccine (Omicron BA.1) minus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was -0.8% with 95% Cis: -9.1%, 7.5% % (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 1.0 with 95% confidence intervals: 0.85, 1.10 (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 3.0% with 95% Cis: -5.5%, 11.5% (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

The following descriptive analyses, obtained for the PP2 Analysis Set, on Day 28 after vaccination provide a longer period of time to assess the magnitude of immune responses against the ancestral (Wuhan) strain:

Monovalent Vaccine (Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 0.8 with 95% confidence intervals: 0.72, 0.93 (the lower limit of the 95% CI around the GMTR was >0.67).

- The estimated percentage difference in SRRs between the monovalent vaccine (Omicron BA.1) and the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)

was -5.5% with 95% CIs: -13.5%, 2.4% (the lower limit of the 95% CI around the percentage difference in SRRs was not >-10%).

Bivalent Vaccine (Original and Omicron BA.1) Descriptive Analysis

- The estimated GMTR of the bivalent vaccine (Original and Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 0.9 with 95% confidence intervals: 0.77, 1.00 (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 -1.6% with 95% CIs: -9.9%, 6.8% (the lower limit of the 95% CI around the percentage difference in SRRs was >-10%).

6.2.2.4 Safety Results: Study 311 Part 1

Study 311 Part 1 safety data included solicited local AEs, solicited systemic AEs, unsolicited AEs, treatment related unsolicited AEs, and a median of 66 days of safety follow up for MAAEs, SAEs, and AESIs.

Table 19 presents an overall summary of solicited and unsolicited AEs.

Table 19. Solicited Adverse Events (Through 7 Days) and Unsolicited Adverse Events (Through 36 Days) After Booster Vaccination With Monovalent (Omicron BA.1), Original Monovalent, or Bivalent (Original and Omicron BA.1) in Adult Participants Previously Received 3 Vaccinations With COVID-19 mRNA Vaccines, Safety Analysis Set

Parameter	Group C Monovalent (Omicron BA.1) N=286	Group D Original Monovalent N=274	Group E Bivalent (Original and Omicron BA.1) N=269
Any solicited AE	230 (81.3)	226 (83.1)	212 (79.1)
Grade 3 or higher	25 (8.8)	11 (4.0)	11 (4.1)
Solicited local AEs[1]	196 (69.3)	193 (71.0)	173 (64.6)
Grade 3 or higher	5 (1.8)	1 (0.4)	3 (1.1)
Solicited systemic AEs	176 (62.2)	158 (58.1)	166 (61.9)
Grade 3 or higher	21 (7.4)	10 (3.7)	8 (3.0)
Any unsolicited AE	98 (34.3)	104 (38.0)	91 (33.8)
Treatment-related	14 (4.9)	8 (2.9)	9 (3.3)
Severe	0	4 (1.5)	0
Treatment-related severe	0	0	0
Any SAE	1 (0.3)	1 (0.4)	0
Treatment-related	0	0	0
Any unsolicited AE leading to vaccination discontinuation	1 (0.3)	1 (0.4)	0
Treatment-related	1 (0.3)	0	0
Any unsolicited AE leading to study discontinuation	0	1 (0.4)	0
Treatment-related	0	0	0
Any MAAE	14 (4.9)	18 (6.6)	13 (4.8)
Treatment-related	1 (0.3)	0	0

Parameter	Group C Monovalent (Omicron BA.1) N=286	Group D Original Monovalent N=274	Group E Bivalent (Original and Omicron BA.1) N=269
Treatment-related serious MAAE	0	0	0
Severe MAAE	0	3 (1.1)	0
Related Severe MAAE	0	0	0
Any AESI: PIMMC[2]	0	1 (0.4)	0
Treatment-related	0	0	0
Any AESI: complications due to COVID-19	0	0	0
Any myocarditis/pericarditis	0	0	0

Source: Study 311 Part 1 Interim Study Report, Table 35, p. 134
Note: Table includes only those participants who completed e-Diary for solicited AEs.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; GMTR=geometric mean titer ratio; MAAE=medically attended adverse event; PIMMC=potential immune-mediated medical condition
1. Injection site reaction; [The numbers N for those who completed e-Diary for solicited reactions are 283 (Group C), 272 (Group D), and 268 (Group E)]. The %s for solicited AEs in the table are based on these Ns. Solicited local and systemic AEs were reported within 7 days (Days 0 to 6) after booster vaccination.
2. PIMMCs were recorded according to protocol-defined criteria and by the investigator reporting in the CRF.
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

Solicited AEs

Table 20 summarizes the solicited local injection site ARs reported by severity.

Table 20. Solicited Local Adverse Events by Severity 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

Parameter	Group C Monovalent (Omicron BA.1) N=283	Group D Original Monovalent N=272	Group E Bivalent (Original and Omicron BA.1) N=268
Any local AE	--	--	--
Any Grade	196 (69.3)	193 (71.0)	173 (64.6)
Grade 3	5 (1.8)	1 (0.4)	3 (1.1)
Grade 4	0	0	0
Pain/tenderness	--	--	--
Any Grade	196 (69.3)	192 (70.6)	173 (64.6)
Grade 3	5 (1.8)	1 (0.4)	2 (0.7)
Grade 4	0	0	0
Pain	--	--	--
Any Grade	110 (38.9)	109 (40.1)	96 (35.8)
Grade 3	2 (0.7)	1 (0.4)	0
Grade 4	0	0	0
Tenderness	--	--	--
Any Grade	181 (64.0)	175 (64.3)	162 (60.4)
Grade 3	3 (1.1)	1 (0.4)	2 (0.7)
Grade 4	0	0	0
Redness	--	--	--
Any Grade[1]	7 (2.5)	3 (1.1)	3 (1.1)
Grade 3	0	0	1 (0.4)
Grade 4	0	0	0

Parameter	Group C Monovalent (Omicron BA.1) N=283	Group D Original Monovalent N=272	Group E Bivalent (Original and Omicron BA.1) N=268
Swelling	--	--	--
Any Grade[1]	7 (2.5)	3 (1.1)	4 (1.5)
Grade 3	0	0	0
Grade 4	0	0	0

Source: Table 36 in the Study 311 Part 1 Interim Study Report, p. 136 .
Note: Table includes only those participants who completed e-Diary solicited AEs.
Abbreviations: AE=adverse event
1. Diameter ≥25 mm.
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 Table 20, frequencies of local injection site ARs were relatively balanced across the 3 vaccine groups, occurring with incidence rates of 69.3%, 71.0%, and 64.6% in the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and Omicron BA.1) groups, respectively. Pain and tenderness were the most common injection site ARs reported, (ranging from 64.6% to 71.0% of participants in each group), with redness and swelling reported in less than 3% of participants.

The median day of onset was Day 1 for pain and tenderness and Day 2 for redness and swelling, with median durations of 1.0 day for pain, redness, and swelling and 2.0 days for pain/tenderness and tenderness.

Solicited Systemic ARs

Table 21 presents a summary of solicited systemic ARs by severity.

Table 21. Solicited Systemic Adverse Events by Severity for 7 Days After Booster Vaccination With Monovalent (Previously Received 3 Vaccinations with COVID-19 mRNA Vaccines, Safety Analysis Set

Parameter	Group C Monovalent (Omicron BA.1) N=283	Group D Original Monovalent N=272	Group E Bivalent (Original and Omicron BA.1) N=268
Any systemic AE	--	--	--
Any Grade	176 (62.2)	158 (58.1)	166 (61.9)
Grade 3	20 (7.1)	10 (3.7)	8 (3.0)
Grade 4	1 (0.4)	0	0
Fever	--	--	--
Any Grade[1]	5 (1.8)	2 (0.7)	1 (0.4)
Grade 3	1 (0.4)	0	0
Grade 4	1 (0.4)	0	0
Fatigue/malaise	--	--	--
Any Grade	127 (44.9)	111 (40.8)	121 (45.1)
Grade 3	15 (5.3)	8 (2.9)	7 (2.6)
Grade 4	0	0	0
Fatigue	--	--	--
Any Grade	115 (40.6)	102 (37.5)	110 (41.0)
Grade 3	11 (3.9)	5 (1.8)	6 (2.2)
Grade 4	0	0	0

Parameter	Group C Monovalent (Omicron BA.1) N=283	Group D Original Monovalent N=272	Group E Bivalent (Original and Omicron BA.1) N=268
Malaise	--	--	--
Any Grade	66 (23.3)	54 (19.9)	51 (19.0)
Grade 3	9 (3.2)	5 (1.8)	2 (0.7)
Grade 4	0	0	0
Muscle pain	--	--	--
Any Grade	71 (25.1)	66 (24.3)	64 (23.9)
Grade 3	5 (1.8)	0	0
Grade 4	0	0	0
Joint pain	--	--	--
Any Grade	27 (9.5)	29 (10.7)	16 (6.0)
Grade 3	2 (0.7)	0	1 (0.4)
Grade 4	0	0	0
Nausea/vomiting	--	--	--
Any Grade	21 (7.4)	19 (7.0)	23 (8.6)
Grade 3	0	1 (0.4)	0
Grade 4	0	0	0
Headache	--	--	--
Any Grade	106 (37.5)	95 (34.9)	96 (35.8)
Grade 3	1 (0.4)	3 (1.1)	1 (0.4)
Grade 4	0	0	0

Source: Table 37 in the Study 311 Part 1 Interim Study Report, p. 138
Abbreviations: AE=adverse event
Note: Table includes only those participants who completed e-Diary 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.
1. Temperature ≥38 C.

As shown in Table 21, the proportions of participants reporting solicited systemic ARs were consistent across the 3 vaccine groups: 62.2%, 58.1%, and 61.9% for the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively. Fatigue, headache, muscle pain, and malaise were the most frequent solicited systemic ARs. Fever was reported in less than 2% of participants.

Grade 3 or higher solicited systemic ARs were reported by 7.1%, 3.7%, and 3.0% of participants for the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively. One solicited systemic grade 4 AR of fever was reported in the monovalent vaccine (Omicron BA.1) group.

Unsolicited AEs

Unsolicited AEs reported through 36 days post-vaccination were balanced across the 3 vaccine groups: 34.3%, 38.0%, and 33.8% of the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) groups, respectively. 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*, occurring in 41 (14.3%), 46 (16.8%), and 56 (20.8%) participants in 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 (3.8%, 5.5%, and 8.6%, respectively) and COVID-19 (4.5%, 4.7%, and 6.7%, respectively). No clear differences between vaccine groups were observed with respect to the incidence of individual AEs.

MAAEs

MAAEs through 36 days after vaccination were most frequently reported in the MedDRA SOC of *Infections and Infestations*: 3.1%, 2.9%, and 3.0% in the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and Omicron BA.1) groups, respectively. Within this SOC, infection with COVID-19 (1.0%, 1.1%, and 0.7%, respectively) was the most frequent MAAE reported. One (0.3%) participant in the monovalent vaccine (Omicron BA.1) group 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 data cut-off (72 days), with an outcome of recovering/resolving.

The percentage of participants reporting MAAEs through 2 months of safety follow-up (median 66 days) after booster vaccination were low and similar between the 3 vaccine groups: 5.9%, 20 7.3%, and 5.6% in the monovalent vaccine (Omicron BA.1), Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and Omicron BA.1) groups, respectively.

Severe MAAEs through 2 months after booster vaccination were reported in 2 participants in the monovalent vaccine (Omicron BA.1) group, 3 (1.1%) participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, and 1 participant in the bivalent vaccine (Original and Omicron BA.1) group. In the in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, the severe MAAEs were anaphylactic reaction (classified as an SAE and described in a narrative summary below), urinary tract infection, and back pain. In the monovalent vaccine (Omicron BA.1) group, the severe MAAEs were breast cancer and depression, both of which were classified as SAEs (narrative summaries below). In the bivalent vaccine (Original and Omicron BA.1) group, the MAAE was cellulitis/ diabetic ulcer and is also classified as an SAE (narrative summary below). None of the severe events were considered related to trial vaccine.

SAEs

There were no deaths in the study. SAEs through 28 days after vaccination were reported by 2 participants. One (0.3%) participant receiving the monovalent vaccine (Omicron BA.1) had dysmenorrhea and 1 (0.4%) participant receiving the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had an anaphylactic reaction due to a nut allergy. Both SAEs were considered unrelated to study vaccine.

Throughout the 2-month data collection period, a total of 7 participants reported 7 SAEs. In the monovalent vaccine (Omicron BA.1) group, SAEs included invasive ductal breast carcinoma, depression, and dysmenorrhea. In the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, SAEs included anaphylactic reaction and gastroenteritis. In the bivalent vaccine (Original and Omicron BA.1) group, SAEs included endometriosis and cellulitis/diabetic ulcer. None of the SAEs were considered related to vaccine by the investigator and Sponsor, and this reviewer agrees with these assessments based on lack of temporal association,

biological implausibility, and/or alternative etiology. Brief details of each SAE are provided below.

- 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 post-vaccination. She subsequently underwent bilateral mastectomy.
- 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 post-vaccination. The participant had a depression exacerbation and was admitted to the hospital and discharged the following day.
- 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 post-vaccination. The participant was hospitalized for pain management and symptoms resolved.
- 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 approximately 11 days post-vaccination after ingesting nuts.
- A 55-year-old White female in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group experienced an SAE of gastroenteritis approximately 46 days post-vaccination. The participant presented to the emergency department with a 1-day history of fever, diarrhea, vomiting, and abdominal pain. She was admitted to the hospital, where stool cultures were obtained and a CT of the abdomen/pelvis revealed probable acute colitis, and she was discharged home the following day. Stool cultures were subsequently negative.
- 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 approximately 54 days post-vaccination. She subsequently underwent laparoscopic surgery for excision of endometriosis.
- A 53-year-old White male in the bivalent vaccine (Original and Omicron BA.1) group with a history of type 2 diabetes mellitus, coronary artery disease, coronary artery bypass graft, myocardial infarction, and left 5th toe infection and amputation experienced SAEs of cellulitis and diabetic ulcer. Approximately 1 week following COVID-19 and 51 days post-vaccination, the participant was diagnosed with right lower limb cellulitis and a diabetic ulcer of the right toe. He was admitted to the hospital and treated with IV antibiotics.

<u>Unsolicited AEs Leading to Vaccine or Study Discontinuation</u>
Two participants experienced AEs leading to study vaccine discontinuation.

- A 44-year-old male in the monovalent vaccine (Omicron BA.1) group reported oropharyngeal pain/ sore throat symptoms described as mild in severity that began on Day 3 and resolved on Day 23 post-vaccination. Symptoms were deemed related to the study vaccine. The decision was made not to administer the second study vaccine.
- A 36-year-old male in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group experienced the onset of acute psychosis on Day 19 post-vaccination 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 subject due to the reported adverse event. Following study discontinuation, follow-up was received noting the subject was under the care of his regular general practitioner and the psychotic episode resolved after starting olanzapine. The event was considered resolved.

AESIs

The SAE of anaphylactic reaction to ingested nuts described above was also categorized as an AESI (PIMMC) (see safety narrative for participant). No other AESIs were reported.

Subgroup Analyses

Adverse event subgroup analyses conducted by sex, race, and ethnicity showed the following:

Solicited local injection site ARs were reported at higher frequencies in female (74.5% to 75.5%) than male (50.4% to 66.4%) participants across the 3 vaccine groups. Solicited local AEs were reported at higher frequencies in White participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and Omicron BA.1) groups (72.0% and 66.2%, respectively) than in Asian participants (61.4% and 56.4%, respectively). 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.

Solicited systemic ARs were reported at similar rates in female (64.1%) and male (60.0%) participants in the monovalent vaccine (Omicron BA.1) group but were reported at higher frequencies by female participants in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and bivalent vaccine (Original and BA.1) groups (68.1% and 68.9%, respectively) than by male participants (47.3% and 53.0%, respectively). Solicited systemic ARs were reported at similar frequencies in White (57.0% to 62.1%) and Asian (56.8% to 66.7%) participants across the 3 vaccine groups, however subgroup analyses for other races were of limited value as there were too few participants of other races. Subgroup analysis by ethnicity was also limited as there were too few participants of other ethnicities.

Unsolicited AEs were reported at similar frequencies between male participants (36.4% to 38.3%) and female participants (30.7% to 39.2%) across the 3 vaccine groups. Unsolicited AEs were reported at higher frequencies in White (35.0% to 39.1%) than Asian (16.2% to 26.7%) participants across the 3 vaccine groups. Subgroup analyses of unsolicited severe AEs were inconclusive as there were too few participants with severe events.

MAAEs were reported at similar frequencies between male (4.2% to 6.1%) and female participants (5.2% to 7.0%), across the 3 vaccine groups. Subgroup analyses by race and ethnicity were of limited value due to too few participants in these subgroups with MAAEs for meaningful comparisons. Subgroup analyses of severe MAAEs were of limited value as there were too few participants with severe events.

Subgroup analyses of SAEs by sex, race, and ethnicity were inconclusive as there were too few participants with serious events.

6.2.2.5 Summary of Findings: Study 311 Part 1

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older not previously vaccinated with a COVID-19 vaccine and the effectiveness of a single-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine is inferred from immunogenicity data from Study 311 Part 1 as follows:

- Based on superior neutralizing antibody responses (as measured by GMTR) and non-inferior SRRs induced by the monovalent vaccine (Omicron BA.1) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), it is reasonable to expect that in individuals 18 years of age and older that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

Additional supportive immunogenicity data includes descriptive noninferior neutralizing antibody responses (as measured by GMTR) induced by the monovalent (Omicron BA.1) compared to the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain, the virus upon which the currently authorized formulation was based. 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 non-inferiority criterion on Day 28 based on descriptive analysis, the successful observed GMTR comparison is reassuring in the context of limitations of SRR comparisons and data from other modified vaccines (monovalent [Omicron BA.5] and bivalent [Original and BA.5 and Original and BA.1]) indicating comparable immune responses by both GMTR and SRR to the ancestral (Wuhan) strain compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). While the bivalent vaccine (Original and BA.1) did not show superiority compared to the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against Omicron BA.1 at the 28-day timepoint in descriptive analyses, 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). Another possible explanation for the difference in immunogenicity between the Original and Omicron BA.1 bivalent vaccine and the Original and Omicron BA.5 bivalent vaccine may involve hybrid immunity of the study population exposed to each of these vaccines. At the time of Omicron BA.5 circulation as a variant of concern, a larger proportion of the population had been vaccinated and exposed to COVID-19 infection, thus increasing hybrid immunity leading to heightened immune responses within that population.[42]

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age not previously vaccinated with a COVID-19 vaccine and the effectiveness of a single-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine is extrapolated from immunogenicity data from Study 311 Part 1 support the as follows:

- The superior neutralizing antibody responses (as measured by GMTR) and non-inferior SRRs induced by the monovalent vaccine (Omicron BA.1) compared with the Novavax

COVID-19 Vaccine, Adjuvanted (Original monovalent) can be extrapolated to adolescents 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) (see Decision Memorandum). Therefore, for adolescents, it is reasonable to expect that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

Data from Study 311 Part 1 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). The monovalent vaccine (Omicron BA.1), the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), and the bivalent vaccine (Original and Omicron BA.1) were well tolerated with an acceptable safety profile when administered as a single dose in previously COVID-19 vaccinated adult participants. 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).[40,41] No new safety concerns were identified.

6.2.3 Study 301 Pediatric Extension

As described above, Study 301 is a Phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of Novavax Covid-19 Vaccine, Adjuvanted (Original monovalent). The sections below summarize interim immunogenicity and safety data from an ongoing Pediatric Extension of Study 301, in which participants who had been previously vaccinated with a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) received a single-dose regimen (3rd dose) of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

6.2.3.1 Study Design: Study 301 Pediatric Extension

The Pediatric Extension of Study 301 is an ongoing 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) administered 3 weeks apart. Following blinded crossover, 2 doses of alternate study material were administered 21 days apart.

In response to the evolving pandemic and related public health recommendations, Novavax modified the protocol for the Pediatric Extension of 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, where 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). An ad hoc analysis was conducted with a randomly selected subset of 220 participants from 58 sites in the U.S. who had completed the Day 28 post-Dose 3 visit. Cleaned and reviewable data for this ad hoc safety and immunogenicity population are available through a data cut-off date of September 7, 2022. Additionally, the Sponsor submitted cleaned datasets for the purposes of verifying SAEs through the data cutoff date of November 12, 2022. The study remains ongoing, with follow-up through 2 years post immunization.

The Endpoints and Objectives for evaluating the safety and efficacy of the 3rd vaccine dose in individuals 12 years through 17 years of age who had previously received two doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) are stated in Table 22.

Table 22**. Study 2019nCoV-301: Adolescent Booster Objectives and Endpoints**

Type	Post-Boost Objectives	Post-Boost Endpoints
Immunogenicity	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).	• Neutralizing antibody titers, serum levels of IgG to SARS-CoV-2 S protein and hACE2 inhibition titers from Immunogenicity Population participants immediately prior to Dose 3 and 28 days post Dose 3 • Positive anti-NP antibody titers at any pre-specified time point following the third (booster) vaccine dose in participants with no intervening symptoms of COVID-19. • Immune response by neutralizing antibody titer and IgG antibody to SARS-CoV-2 rS protein and by hACE2 inhibition titers compared in the same participants 28 days Post Dose 3 with 14 days post Dose 2 of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).
Safety	• 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.	• Reactogenicity incidence and severity (mild, moderate, or severe) recorded by all participants on their electronic patient-reported outcome diary application (eDiary) on the day of Dose 3 and subsequent 6 days. • Incidence and severity of unsolicited AEs through 28 days after Dose 3. • Incidence and severity of MAAEs attributed to study vaccine, SAEs, and AESIs. • Death due to any cause.

Source: Protocol 2019nCoV-301: Adolescent Booster Report, Table 1, Page 15
Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; eDiary=electronic patient-reported outcome diary; hACE2=human angiotensin-converting enzyme 2; IgG=immunoglobulin G; MAAE=medically

attended adverse event; NIH=National Institutes of Health; NP=nucleoprotein; PCR=polymerase chain reaction; rS=recombinant spike (protein); SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 rS=severe acute respiratory syndrome coronavirus 2 recombinant spike protein nanoparticle vaccine.

Primary Immunogenicity Evaluation

The effectiveness of a 3rd dose of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was inferred based on a comparison of neutralizing antibody response at Day 28 post-Dose 3 (hereafter referred to as "D28-PD3") with 14 days post-Dose 2 (hereafter referred to as "D14-PD2").

Statistical success criteria included the following:

- Point estimate of the GMR (GMT D28-PD3 /GMT D14-PD2) ≥0.83
- Lower limit of the two-sided 95% CI of the GMFR) >0.67
- Lower limit of the 95% CI of the percentage difference in Serum Conversion Rates (SCRs) (SCR D28-PD3 – SCR D14-PD2) >−10%, where the SCR is defined as the proportion of participants with post-vaccination levels ≥4-fold higher than the baseline levels

Neutralizing antibody titers against ancestral (Wuhan) strain were measured using a validated microneutralization assay (neutralizing antibody titer [MN_{50}] against SARS-CoV-2 wild-type virus).

Immunogenicity Population

Of the 220 participants randomly selected for the ad hoc analyses (~110 each from Cohorts 1 and 2), the Per- Protocol Immunogenicity Analysis Set (PP-IMM) was determined for each study visit and included participants that had a serum sample result available at tested visits and had no major protocol violations that were considered clinically relevant to impact immunological measures at the visit in question, defined as the Ad Hoc Booster PP-IMM Analysis Set. Blood samples for Dose 3 immunogenicity analyses were collected at the time of Dose 3 and at 28 days post-Dose 3. Post-Dose 2 immunogenicity data were collected only in the pre-crossover period and are thus available only for those participants who received Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) prior to crossover (Cohort 2). Therefore, to allow assessments of 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), only participants in Cohort 2 were included in the population used for primary immunogenicity analyses (Cohort 2 Ad Hoc Booster PP-IMM Analysis Set). The Cohort 2 ad hoc Booster PP-IMM analysis set included participants who received 2 doses (0.5 mL 3 weeks apart) of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the initial vaccination period, had an immunogenicity blood sample collected on D14-PD2 and D28-PD3, did not have serologic or virologic evidence (if available) of SARS-CoV-2 infection up to 28 days post Dose 3, did not receive an emergency use authorized COVID-19 vaccine, received Dose 3, and remained blinded on study and without major protocol deviations within 28 days post-Dose 3. This set was comprised of 58 participants, 53 of whom who were assessed for neutralizing antibody against SARS-CoV-2 wild-type virus (Wuhan strain).

Safety Analysis Population

The safety review was based on two analysis populations:

1. The Ad-Hoc Booster Safety Analysis Set from the Protocol 2019nCoV-301: Adolescent Booster Report, which included all the randomly selected 220 subjects from the ad hoc

analyses. This population included only subjects with “cleaned data” with safety follow-up through a data cutoff date of September 7, 2022 with a median safety follow-up of 135 days.

2. Booster Safety Analysis Set from Protocol 2019nCoV-301: 6-Month Booster Safety Addendum to the 12-Month Adolescent Clinical Study Report, which constitutes the entire safety population (n=1499) in previously COVID-19 vaccinated participants 12 years through 17 years of age who received a single-dose regimen (3rd dose) of Novavax COVID-19 Vaccine, Adjuvanted (Original Monovalent), with a data cutoff date of November 12, 2022 and with a median safety follow-up of 6.6 months. This analysis analyzed SAEs, MAAEs, AESIs, and AEs Leading to Study Discontinuation, and provided a subgroup safety analysis.

Safety Analysis Plan

All AEs were coded by primary SOC and PT using the latest version of MedDRA. The version of MedDRA was 23.1 and was later updated to version 25.0. The safety analysis for the Ad-Hoc Booster Safety Analysis Set included all solicited AEs through day 6 post-Dose 3; unsolicited AEs through 28 days post-Dose 3; and all severe AEs and all related AEs, MAAEs, SAEs, AESIs, Deaths, AEs leading to study discontinuation, and COVID-related AEs through the data extraction dates (September 7, 2022). The Booster Safety Analysis Set was used to analyze SAEs, MAAEs, AESIs, Deaths, and AEs Leading to Study Discontinuation through the data extraction of November 12, 2022. A subgroup safety analysis was also conducted on the Booster Safety Analysis Set.

6.2.3.2 Demographics and Disposition: Study 301 Adolescent Single Dose

The demographics and baseline characteristics for the Full Booster Safety Analysis population is summarized in Table 23.

Table 23. Demographic and Baseline Characteristics of the Full Booster Safety Population in the Pediatric Expansion, Full Booster Safety Analysis Set

Parameter	Original Monovalent Booster N=1499
Sex	--
Male	806 (53.8)
Female	693 (46.2)
Age (years)	--
Mean (SD)	13.8 (1.41)
Median	14.0
Minimum-maximum	12-17
Age group	--
12 to <15 years	1020 (68.0)
15 to <18 years	479 (32.0)
Race	--
White	1096 (73.1)
Black or African American	219 (14.6)
Mixed origin (multiple)	77 (5.1)
Asian	53 (3.5)
American Indian or Alaska Native	40 (2.7)
Native Hawaiian or other Pacific Islander	5 (0.3)
Not reported	9 (0.6)

Parameter	Original Monovalent Booster N=1499
Ethnicity	--
Not Hispanic or Latino	1220 (81.4)
Hispanic or Latino	276 (18.4)
BMI (kg/m^2)	--
Mean (SD)	24.41 (7.141)
Median	22.80
Minimum-maximum	10.3 – 63.8
BMI (kg/m^2) category[1]	--
Underweight	48 (3.2)
Healthy weight	759 (50.6)
Overweight	255 (17.0)
Obese	437 (29.2)
SARS-CoV-2 serostatus[2]	--
Anti-NP	--
Positive	772 (51.5)
Negative	405 (27.0)
Missing	322 (21.5)
PCR	--
Negative	1478 (98.6)
Positive	21 (1.4)
Anti-NP / PCR[3]	--
Positive	789 (52.6)
Negative	400 (26.7)
Missing	310 (20.7)

Source: Adolescent Booster Report, Table 9, Page 35
Abbreviations: BMI=body mass index; NP=nucleoprotein; PCR=polymerase chain reaction; SD=standard deviation.
1. BMI was classified as follows (using gender and age specific percentiles): Underweight=participants less than the 5th percentile; Healthy weight=participants within the 5th percentile and up to the 85th percentile; Overweight=participants within the 85th percentile to less than the 95th percentile; Obesity=participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.
2. SARS-CoV-2 serostatus is presented for baseline corresponding to booster dose.
3. Participants with either positive anti-NP or positive PCR are reported as positive. Participants with both negative anti-NP and negative PCR are reported as negative.
Note: Values are presented as n (%) unless otherwise specified.

The proportions of male (53.8%) and female (46.2%) adolescents were balanced. Of the 1499 Dose 3 recipients, 1096 (73.1%) were White, 219 (14.6%) were Black or African American, 77 (5.1%) were Mixed Origin (Multiple), 53 (3.5%) were Asian, 40 (2.7%) were American Indian or Alaska Native, 5 (0.3%) were Native Hawaiian or Other Pacific Islander, 9 (0.6%) were not reported, and 276 (18.4%) were Hispanic or Latino, which is generally consistent with the demographics of the US population. The median age was 14.0 years, and 437 (29.2%) of the subjects were obese. A total of 1478 (98.6%) subjects were PCR negative for SARS-CoV-2, and 789 participants (52.6%) were anti-NP and PCR-negative for SARS-CoV-2. The median time interval between the completion of the 2-dose series (i.e., the primary series) and Dose 3 was 10 months for this population.

The demographics and baseline characteristics for the Ad Hoc Booster Safety Analysis Set for both Cohort 1 and Cohort 2 are summarized in Table 24.

Table 24. Demographic and Baseline Characteristics of the Ad Hoc Booster Analysis Set in the Pediatric Expansion, Ad Hoc Booster Safety Analysis Set

Parameter	Original Monovalent Booster Cohort 1 + Cohort 2 N=220
Sex, n (%)	--
Male	127 (57.7)
Female	93 (42.3)
Age (years)	--
Mean (SD)	14.1 (1.51)
Median	14.0
Minimum-maximum	12-17
Age group, n (%)	--
12 to <15 years	118 (53.6)
15 to <18 years	102 (46.4)
Race, n (%)	--
White	186 (84.5)
Black or African American	12 (5.5)
Mixed origin (multiple)	12 (5.5)
Asian	7 (3.2)
American Indian or Alaska Native	1 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.5)
Not reported	1 (0.5)
Ethnicity, n (%)	--
Not Hispanic or Latino	184 (83.6)
Hispanic or Latino	36 (16.4)
BMI (kg/m^2)	--
Mean (SD)	23.13 (6.031)
Median	21.65
Minimum-maximum	14.2-46.0
BMI (kg/m^2) category[1], n (%)	--
Underweight	12 (5.5)
Healthy weight	125 (56.8)
Overweight	30 (13.6)
Obese	53 (24.1)
SARS-CoV-2 serostatus[2], n (%)	--
Anti-NP	--
Negative	131 (59.5)
Positive	86 (39.1)
Missing	3 (1.4)
PCR, n (%)	--
Negative	220 (100)
Positive	0
Anti-NP / PCR[3], n (%)	--
Negative	131 (59.5)
Positive	86 (39.1)
Missing	3 (1.4)

Source: Adolescent Booster Report, Table 9, Page 36

Abbreviations: BMI=body mass index; NP=nucleoprotein; PCR=polymerase chain reaction; SD=standard deviation.

1. BMI was classified as follows (using gender and age specific percentiles): Underweight=participants less than the 5th percentile; Healthy weight=participants within the 5th percentile and up to the 85th percentile; Overweight=participants within the 85th percentile to less than the 95th percentile; Obese=participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.
2. SARS-CoV-2 serostatus is presented for baseline corresponding to booster dose.
3. Participants with either positive anti-NP or positive PCR are reported as positive. Participants with both negative anti-NP and

negative PCR are reported as negative.

In general, the demographics of the Ad Hoc Booster Safety Analysis Set is generally consistent with and representative of the demographics of the Full Booster Safety Population.

The demographics and baseline characteristics for the Cohort 2 Ad Hoc Booster PP-IMM analysis set is summarized in Table 25.

Table 25. Demographic and Baseline Characteristics of the Ad Hoc Booster Analysis in the Pediatric Expansion, Cohort 2 Ad Hoc Booster PP-IMM Analysis Set

Parameter	Original Monovalent Booster Cohort 2 N=58
Sex, n (%)	--
Male	30 (51.7)
Female	28 (48.3)
Age (years)	--
Mean (SD)	14.0 (1.47)
Median	14.0
Minimum–maximum	12-17
Age group, n (%)	-
12 to <15 years	33 (56.9)
15 to <18 years	25 (43.1)
Race, n (%)	--
White	53 (91.4)
Mixed origin (multiple)	3 (5.2)
Black or African American	1 (1.7)
Asian	1 (1.7)
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0
Not reported	0
Ethnicity, n (%)	-
Not Hispanic or Latino	48 (82.8)
Hispanic or Latino	10 (17.2)
BMI (kg/m^2)	-
Mean (SD)	23.16 (5.416)
Median	21.90
Minimum–maximum	14.3-34.2
BMI (kg/m^2) category[1], n (%)	--
Underweight	2 (3.4)
Healthy weight	34 (58.6)
Overweight	6 (10.3)
Obese	16 (27.6)
SARS-CoV-2 serostatus[2], n (%)	--
Anti-NP	--
Negative	57 (98.3)
Positive	0
Missing	1 (1.7)
PCR, n (%)	--
Negative	58 (100)
Positive	0

Parameter	Original Monovalent Booster Cohort 2 N=58
Anti-NP / PCR[3], n (%)	--
Negative	57 (98.3)
Positive	0
Missing	1 (1.7)

Source: 2019nCoV-301: Adolescent Booster Report, Table 10, Page 39
Abbreviations: BMI=body mass index; NP=nucleoprotein; PCR=polymerase chain reaction; PP-IMM=Per-Protocol Immunogenicity; SD=standard deviation.
1. BMI was classified as follows (using gender and age specific percentiles): Underweight=participants less than the 5th percentile; Healthy weight=participants within the 5th percentile and up to the 85th percentile; Overweight=participants within the 85th percentile to less than the 95th percentile; Obese=participants equal to or greater than the 95th percentile. Percentiles are assigned via Centers for Disease Control and Prevention reference data and cdc-source-code.sas.
2. SARS-CoV-2 serostatus is presented for baseline corresponding to booster dose.
3. Participants with either positive anti-NP or positive PCR are reported as positive. Participants with both negative anti-NP and negative PCR are reported as negative.

In general, the demographics of the Cohort 2 Ad Hoc Booster PP-IMM Analysis Set are generally consistent with and representative of the demographics of the Full Booster Safety Population.

The median duration between Dose 2 and Dose 3 of Novavax COVID-19 Vaccine (Original monovalent) was 10.6 months in Cohort 2 and 7.7 months in Cohort 1.

6.2.3.3 Immunogenicity Results: Study 301 Adolescent Single Dose

The effectiveness of a single-dose regimen (3rd dose) of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age who had previously received the 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was inferred based on a comparison of neutralizing antibody response at D28-PD3 versus D14-PD2, as shown in Table 26.

Table 26. Comparison of Neutralizing Antibody Titers (MN50) Against SARS-CoV-2 Wild-Type Virus (Ancestral [Wuhan] strain) at 28 Days After the Third (Booster) Dose of Original Monovalent Versus at 14 Days After the Second Dose of Original Monovalent (Primary Series) in the Pediatric Expansion, Cohort 2 Ad Hoc Booster PP-IMM Analysis Set

Original Monovalent 28 Days PD3 Cohort 2 GMT N=53 (95% CI)[1]	Original Monovalent 14 Days PD2 Cohort 2 GMT N=53 (95% CI)[1]	28 Days PD3/ 14 Days PD2 GMFR[3] (95% CI)[1]	Met Success Criterion[2]
11824.4 (8993.1, 15546.9)	4434.0 (3658.0, 5374.5)	2.7 (2.0, 3.5)	Yes, met success criterion

Source: 2019nCoV-301: Adolescent Booster Report, Table 11, Page 41
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%; PD2=post-Dose 2; PD3=post-Dose 3.
1. The 95% CI for GMT and GMFR were calculated based on the t-distr bution of the log-transformed values, then back transformed to the original scale for presentation.
2. Noninferiority of the single booster dose of Original monovalent was achieved if 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 in Cohort 2 was >0.67 and the point estimate was >0.83.
3. GMFR is defined as the GMT ratio of post-boost GMT / post-primary Day 35 GMT.
Note: The median duration between Dose 2 of Original monovalent and Dose 3 in Cohort 2 was 10.6 months.

The lower bound of the 2-sided 95% confidence interval for GMFR was 2.0, which was greater than 0.67, and the GMFR estimate was 2.7, which was greater than 0.83, demonstrating noninferiority of the immune response after a single-dose regimen of the Novavax COVID-19

Vaccine, Adjuvanted (Original monovalent) in previously vaccinated individuals 12 years through 17 years of age, as measured by GMTR, compared with a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in previously unvaccinated individuals 12 years through 17 years of age.

The SCRs for neutralizing antibody titers (MN_{50}) against the ancestral (Wuhan) strain 28 days post-Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) compared with 14 days post-Dose 2 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for the Cohort 2 Ad Hoc Booster PP-IMM Analysis Set are presented in Table 27.

Table 27. Seroconversion Rates for Neutralizing Antibody Titers (MN50) Against SARS-CoV-2 Wild-Type Virus (Ancestral [Wuhan] Strain) at 28 Days After the Third (Booster) Dose of Original Monovalent Versus at 14 Days After the Second Dose of Original Monovalent (Primary Series in the Pediatric Expansion, Cohort 2 Ad Hoc Booster PP-IMM Analysis Set

Original Monovalent 28 Days PD3 Cohort 2 N=53 % SCR (95% CI)[1]	Original Monovalent 14 Days PD2 Cohort 2 N=53 % SCR (95% CI)[1]	28 Days PD3-14 Days PD2 Difference in SCRs[2], % (95% CI)[3]	Met Success Criterion[4]
100 (93.3, 100)	100 (93.3, 100)	0.0 (-6.8, 6.8)	Yes, met success criterion

Source: 2019nCoV-301: Adolescent Booster Report, Table 12, Page 44
Abbreviations: CI=confidence interval; LB=lower bound; MN_{50}=microneutralization assay with an inhibitory concentration of 50%; N=number of participants in the assay-specific Ad Hoc Booster PP-IMM Analysis Set; SCR=seroconversion rate.
1. Based on Clopper-Pearson.
2. Percentage difference in SCR 28 days post-Dose 3 minus SCR 14 days post-Dose 2 of Original monovalent in Cohort 2.
3. Tango method.
4. Success criterion: LB of 95% CI >-10%
Note: SCR was defined as the proportion of participants with post-vaccination levels ≥4-fold higher than the baseline levels. Note: The median duration between Dose 2 and Dose 3 of Original monovalent in Cohort 2 was 10.6 months (Table 26).

The lower bound of the 2-sided 95% confidence interval for percentage difference in SCRs was -6.8%, which was greater than -10%, demonstrating noninferiority of the immune response after a single-dose regimen of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in previously vaccinated individuals 12 years through 17 years of age, as measured by SCR, compared with a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in previously unvaccinated individuals 12 years through 17 years of age.

Immunogenicity Analysis Conclusions

Emergency Use Authorization (EUA) of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in previously unvaccinated individuals 12 years through 17 years of age (i.e., the “primary series”) was based on data from the Pediatric Extension of Study 301 which demonstrated 78.3% (95% CI: 37.6%, 92.5%) efficacy against PCR-confirmed symptomatic mild, moderate or severe COVID-19 from 7 days post-Dose 2 (see Decision Memorandum). Given that the noninferiority criteria for the GMFR lower bound of the 95% CI, the GMFR point estimate, and percentage difference in SCRs were met when the immune responses after a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine were compared with the immune responses after a 2-dose series in individuals 12 years through 17 years of age who were not previously vaccinated, it is reasonable to infer the effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine.

6.2.3.4 Safety Results: Study 301 Adolescent Single Dose

The duration of safety follow-up for the Dose 3 vaccination period for the Ad Hoc Booster Safety Analysis Set is presented in Table 28.

Table 28. Duration of Safety Follow-Up for the Dose 3 Vaccination Period, Ad Hoc Booster Safety Analysis Set

Parameter	Original Monovalent Cohort 1 N=110	Original Monovalent Cohort 2 N=110	Original Monovalent Cohort 1 + 2 N=220
Median follow-up post-Dose 3, days	134	136	135
Completed at least 1 month follow-up post-Dose 3, n (%)	110 (100)	109 (99.1)	219 (99.5)
Completed at least 2 months follow-up post-Dose 3, n (%)	110 (100)	109 (99.1)	219 (99.5)

Source: Table 14.3.8.2u
Note: Follow up post-booster is defined as the time from Dose 3 date to the earliest date of early termination, date of death and date of data cut (September 7, 2022).
Note: Data reported as of the data cut-off date of September 7, 2022.

For the Dose 3 vaccination period, as of June 16, 2022, median follow-up after Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 51 days for Cohort 1, 53 days for Cohort 2, and 52 days for Cohort 1 + Cohort 2 combined, with approximately 19% of participants in Cohort 1 + Cohort 2 combined being followed for at least 2 months after Dose 3 for the Ad Hoc Booster Safety Analysis Set.

Table 29. Duration of Safety Follow-Up for the Dose 3 Vaccination Period, Booster Safety Analysis Set

Parameter	Original Monovalent Cohort 1 N=490	Original Monovalent Cohort 2 N=1009	Original Monovalent Cohort 1 + 2 N=1499
Completed Dose 3	490	1009	1499
Median follow-up post-Dose 3 (days)	134	135	135
Completed at least 1 month follow-up post-Dose 3, n (%)	490 (100)	1008 (99.9)	1498 (99.9)
Completed at least 2 months follow-up post-Dose 3, n (%)	482 (98.4)	1001 (99.2)	1483 (98.9)

Source: 2019nCoV-301: Adolescent Booster Report, Table 28, Page 73
Note: Follow up post-Dose 3 is defined as the time from Dose 3 date to the earliest date of early termination, date of death and date of data cut (September 07, 2022).
Note: Data reported as of the data extract date of September 07, 2022

The median follow-up through the data extract date of September 7, 2022 for the 1,499 participants who received Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 134 days (range of 33 to 156 days) for Cohort 1, 135 days (range of 30 to 157 days) for Cohort 2, and 135 days (range of 30 to 157 days) for Cohort 1 + Cohort 2 combined, with 98.9% of participants in Cohort 1 + Cohort 2 combined being followed for at least 2 months after Dose 3 vaccination.

Ad-Hoc Booster Safety Analysis Set Analysis from the Protocol 2019nCoV-301: Adolescent Booster Report (Data Cutoff of September 7, 2022)

Solicited ARs

The summary of the solicited local and systemic ARs by maximum toxicity grade within 7 days after Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for Cohorts 1 and 2 combined for the Ad Hoc Booster Safety Analysis Set is presented in Table 30.

Table 30. Solicited Local and Systemic Adverse Reactions Within 7 Days After Dose 3 of Original Monovalent (Cohort 1 and Cohort 2 Combined) in the Pediatric Expansion, Ad Hoc Booster Safety Analysis Set

Solicited Reaction, n (%)	Original Monovalent Cohort 1 + Cohort 2 N=190
Any solicited reaction	--
Any (grade ≥1)	172 (90.5)
Grade 3	77 (40.5)
Injection site reaction	--
Any (grade ≥1)	153 (80.5)
Grade 3	23 (12.1)
Pain/tenderness	--
Any (grade ≥1)	153 (80.5)
Grade 3	20 (10.5)
Pain	--
Any (grade ≥1)	121 (63.7)
Grade 3	8 (4.2)
Tenderness	--
Any (grade ≥1)	136 (71.6)
Grade 3	15 (7.9)
Erythema (redness)	--
Any (grade ≥1)	20 (10.5)
Grade 3	4 (2.1)
Swelling	--
Any (grade ≥1)	19 (10.0)
Grade 3	2 (1.1)
Systemic reaction	--
Any (grade ≥1)	163 (85.8)
Grade 3	70 (36.8)
Fever	--
Any (grade ≥1)	44 (23.2)
Grade 3	12 (6.3)
Fatigue/malaise	--
Any (grade ≥1)	132 (69.5)
Grade 3	55 (28.9)
Fatigue	--
Any (grade ≥1)	125 (65.8)
Grade 3	45 (23.7)
Malaise	--
Any (grade ≥1)	89 (46.8)
Grade 3	31 (16.3)
Myalgia (muscle pain)	--
Any (grade ≥1)	117 (61.6)
Grade 3	26 (13.7)

Solicited Reaction, n (%)	Original Monovalent Cohort 1 + Cohort 2 N=190
Arthralgia (joint pain)	--
Any (grade ≥1)	43 (22.6)
Grade 3	9 (4.7)
Nausea/vomiting	--
Any (grade ≥1)	50 (26.3)
Grade 3	5 (2.6)
Headache	--
Any (grade ≥1)	130 (68.4)
Grade 3	25 (13.2)

Source: 2019nCoV-301: Adolescent Booster Report, Table 29, Page 75
Abbreviations: AR=adverse reaction; n=number of participants who reported at least 1 AR; N=number of participants who received the booster dose and completed at least 1 day of the post-booster dose reactogenicity diary; U.S. FDA=United Stated Food and Drug Administration.
Note: Per U.S. FDA request, solicited local Adverse Reactions of pain and tenderness (pain/tenderness) and solicited systemic Adverse Reactions of fatigue and malaise (fatigue/malaise) were combined due to similarities in the respective paired terms.
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.

Any (Grade ≥1) solicited reactions were reported by 172 participants (90.5%), 77 (40.5%) of whom reported Grade 3 reactions. Each solicited local and systemic reaction was reported by at least 10% of participants. The most frequently reported (>25% participants) ARs included: local tenderness and pain (80.5% of participants) and headache (68.4% of participants), fatigue (65.8% of participants), muscle pain (61.6% of participants), malaise (46.8% of participants), and nausea/vomiting (26.3% of participants). The most frequently reported Grade 3 ARs included fatigue (23.7% of participants) and malaise (16.3% of participants). No Grade 4 ARs were reported.

The summary of solicited local and systemic adverse events by maximum toxicity grade within 7 days after Dose 1, Dose 2, and Dose 3 of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in Cohort 2 Population Ad Hoc Booster Safety Analysis Set is presented in Table 31.

Table 31. Solicited Local and Systemic Adverse Reactions Within 7 Days after Primary and Booster Vaccination of Original Monovalent in Cohort 2 in the Pediatric Expansion, Ad Hoc Booster Safety Analysis Set

Solicited Reaction, n (%)	Original Monovalent Primary Cohort 2 Dose 1 N=109	Original Monovalent Primary Cohort 2 Dose 2 N=107	Original Monovalent Booster Cohort 2 Dose 3 N=97
Any solicited reaction	88 (80.7)	95 (88.8)	87 (89.7)
Injection site reaction	--	--	--
Any (grade ≥1)	73 (67.0)	83 (77.6)	82 (84.5)
Grade 3	1 (0.9)	4 (3.7)	15 (15.5)
Pain/tenderness	--	--	--
Any (grade ≥1)	72 (66.1)	83 (77.6)	82 (84.5)
Grade 3	1 (0.9)	3 (2.8)	14 (14.4)
Pain	--	--	--
Any (grade ≥1)	47 (43.1)	62 (57.9)	65 (67.0)
Grade 3	1 (0.9)	1 (0.9)	6 (6.2)

Solicited Reaction, n (%)	Original Monovalent Primary Cohort 2 Dose 1 N=109	Original Monovalent Primary Cohort 2 Dose 2 N=107	Original Monovalent Booster Cohort 2 Dose 3 N=97
Tenderness	--	--	--
Any (grade ≥1)	63 (57.8)	74 (69.2)	73 (75.3)
Grade 3	0	2 (1.9)	10 (10.3)
Erythema (redness)	--	--	--
Any (grade ≥1)	1 (0.9)	6 (5.6)	9 (9.3)
Grade 3	0	1 (0.9)	2 (2.1)
Swelling	--	--	--
Any (grade ≥1)	3 (2.8)	9 (8.4)	7 (7.2)
Grade 3	0	1 (0.9)	2 (2.1)
Systemic reaction	--	--	--
Any (grade ≥1)	58 (53.2)	82 (76.6)	83 (85.6)
Grade 3	3 (2.8)	26 (24.3)	33 (34.0)
Grade 4	0	1 (0.9)	0
Fever	--	--	--
Any (grade ≥1)	2 (1.8)	24 (22.4)	19 (19.6)
Grade 3	0	3 (2.8)	6 (6.2)
Fatigue/malaise	--	--	--
Any (grade ≥1)	36 (33.0)	68 (63.6)	69 (71.1)
Grade 3	3 (2.8)	21 (19.6)	28 (28.9)
Fatigue	--	--	--
Any (grade ≥1)	31 (28.4)	62 (57.9)	66 (68.0)
Grade 3	2 (1.8)	15 (14.0)	23 (23.7)
Malaise	--	--	--
Any (grade ≥1)	20 (18.3)	49 (45.8)	49 (50.5)
Grade 3	1 (0.9)	10 (9.3)	14 (14.4)
Myalgia (muscle pain)	--	--	--
Any (grade ≥1)	32 (29.4)	52 (48.6)	62 (63.9)
Grade 3	1 (0.9)	5 (4.7)	12 (12.4)
Arthralgia (joint pain)	--	--	--
Any (grade ≥1)	6 (5.5)	21 (19.6)	25 (25.8)
Grade 3	0	3 (2.8)	6 (6.2)
Nausea/vomiting	--	--	--
Any (grade ≥1)	9 (8.3)	24 (22.4)	29 (29.9)
Grade 3	0	0	2 (2.1)
Grade 4	0	1 (0.9)	0
Headache	--	--	--
Any (grade ≥1)	40 (36.7)	70 (65.4)	68 (70.1)
Grade 3	0	6 (5.6)	13 (13.4)

Source: 2019nCoV-301: Adolescent Booster Report, Table 30, Page 76
Abbreviations: AR=adverse reaction; n=number of participants who reported at least 1 AR; N=number of participants in the Safety Analysis set within Cohort 2 who received Dose 1, Dose 2, and Dose 3 and completed at least 1 day of the reactogenicity diary; U.S. FDA=United Stated Food and Drug Administration.
Note: Per U.S. FDA request, solicited local Adverse Reactions of pain and tenderness (pain/tenderness) and solicited systemic Adverse reactions of fatigue and malaise (fatigue/malaise) were combined due to similarities in the respective paired terms.
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.
Note: Values are presented as n (%) unless otherwise specified; percentages are based on n/1 × 100.

Frequencies of solicited local and systemic adverse reactions in Cohort 2, any grade (grade ≥1) and grade ≥3, generally increased with each successive dose of the Novavax COVID-19

Vaccine, Adjuvanted (Original monovalent) with most adverse events being grade 1 or grade 2 in severity. Reactogenicity appeared to increase between Dose 2 and Dose 3 for both local solicited AEs (83 [77.6%] for Dose 2 versus 82 [84.5%] for Dose 3) and systemic solicited AEs (82 [76.6%] for Dose 2 versus 83 [85.6%] for Dose 3). Tenderness and pain (82 [84.5%]) was the most frequent solicited local AE, and muscle pain (62 [63.9%]), fatigue (66 [68.0%]), headache (68 [70.1%]), and malaise (49 [50.5%]) were the most frequent solicited systemic adverse reactions.

Dose 3 of Novavax COVID-19 Vaccine (Original monovalent) elicited higher numbers of several systemic solicited adverse reactions in individuals 12 years through 17 years of age (adolescents) compared to individuals 18 years and older (see Decision Memorandum). Adolescents had higher numbers of fevers (greater than 2 times higher as those reported in adults), nausea or vomiting, and headaches, suggesting that this vaccine may be slightly more reactogenic in adolescents compared to adults. Additionally, adolescents had substantially higher grade 3 local and solicited systemic adverse reactions with each succeeding dose of vaccine. The percentage of subjects reporting grade 3 reactions for injection site reaction, pain/ tenderness, any systemic reaction, fever, fatigue/malaise, myalgia, arthralgia and headache were approximately 3-5 times higher with dose two compared to dose one and ten times higher with Dose 3 compared to Dose 1.

Unsolicited AEs

Unsolicited AEs through 28 days post-Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) were reported in 11 (5.0%) adolescent participants, who experienced 13 events. AEs of lymphadenopathy and oropharyngeal pain were reported by 2 (0.9%) participants each, with the remainder of AEs reported by 1 participant each. All of the AEs were mild to moderate in severity, with the exception of a severe and serious event of cholelithiasis. Of the 13 events, 4 were considered related, including lymphadenopathy (n=2), body temperature increased, and oropharyngeal pain.

Medically Attended Adverse Events, Adverse Events of Special Interest, Adverse Events Leading to Discontinuation, and Serious Adverse Events.

MAAEs through 28 days post-Dose 3 of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) included a severe and serious event of cholelithiasis, and moderate events of upper respiratory tract infection, and a hand fracture.

There were no AEs leading to study discontinuation, resulting in death, or AESIs.

One (0.5%) participant reported an SAE: A 16-year-old White Hispanic or Latino female with a history of gastroesophageal reflux disease and a body mass index (BMI) of 25.4 kg/m^2 experienced a single episode of cholelithiasis 99 days post-Dose 3. The participant was hospitalized and underwent an elective scheduled laparoscopic cholecystectomy, after which the event was considered resolved. Although the Principal Investigator did not provide an alternative etiology for the event of cholelithiasis, the Principal Investigator assessed the event of cholelithiasis as not related to the study vaccine. The Sponsor assessed the event of cholelithiasis as not related to the study vaccine based on biologic implausibility.

> *Clinical Reviewer Comment: Based on the participant's risk factors and timing of the event (i.e., lack of a temporal link), it is unlikely that the study vaccine caused the episode of cholelithiasis. However, at the time of this review, cholelithiasis has been reported in adults in other clinical trials of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and*

is discussed in the EUA review memo for the authorization of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum). Based on this single case and in the absence of a placebo comparator, there is insufficient evidence to establish or exclude a causal relationship between the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and events of cholelithiasis.

Booster Safety Analysis Set

In this analysis, data from the Protocol 2019nCoV-301: 6-Month Booster Safety Addendum to the 12-Month Adolescent Clinical Study Report were provided through the data cutoff date of November 12, 2022, with a median safety follow-up of 6.6 months.

Serious Adverse Events

The frequencies of SAEs in all participants from Dose 3 with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) through 28 days post-Dose 3 after and from Dose 3 through the data cutoff date (Booster Safety Analysis Set and Safety Analysis Set) are presented in Table 32, and summarized in the text below.

Table 32. Frequencies of Serious Adverse Events in All Participants From Dose 3 With Original Monovalent Through 28 Days Post-Dose 3 and From Dose 3 Through the Data Cutoff Date, Booster Safety Analysis Set and Safety Analysis Set

System Organ Class/Preferred Term MedDRA Version 25.0	Original Monovalent Dose 3 Through 28 Days Post-Dose 3 N=1499 n (%)	Original Monovalent Dose 3 Through Data Cutoff Date[1] N=1499 n (%)
Any SAE	2 (0.1)	19 (1.3)
Psychiatric disorders	1 (<0.1)	9 (0.6)
Suicide attempt	1 (<0.1)	1 (<0.1)
Acute stress disorder	0	1 (<0.1)
Aggression	0	1 (<0.1)
Anxiety	0	1 (<0.1)
Attention deficit hyperactivity disorder	0	1 (<0.1)
Depression	0	1 (<0.1)
Depression suicidal	0	1 (<0.1)
Intentional self-injury	0	1 (<0.1)
Major depression	0	1 (<0.1)
Oppositional defiant disorder	0	1 (<0.1)
Suicidal ideation	0	1 (<0.1)
Injury, poisoning and procedural complications	0	3 (0.2)
Femur fracture	0	1 (<0.1)
Concussion	0	1 (<0.1)
Extradural hematoma	0	1 (<0.1)
Intentional overdose	0	1 (<0.1)
Patella fracture	0	1 (<0.1)
Road traffic accident	0	1 (<0.1)
Subdural hematoma	0	1 (<0.1)
Wrist fracture	0	1 (<0.1)
Hepatobiliary disorders	0	2 (0.1)
Bile duct stone	0	1 (<0.1)
Cholelithiasis	0	1 (<0.1)

System Organ Class/Preferred Term MedDRA Version 25.0	Original Monovalent Dose 3 Through 28 Days Post-Dose 3 N=1499 n (%)	Original Monovalent Dose 3 Through Data Cutoff Date[1] N=1499 n (%)
Metabolism and nutrition disorders	1 (<0.1)	1 (<0.1)
Type 2 diabetes mellitus	1 (<0.1)	1 (<0.1)
Nervous system disorders	0	1 (<0.1)
Loss of consciousness	0	1 (<0.1)
Gastrointestinal disorders	0	1 (<0.1)
Pancreatitis	0	1 (<0.1)
Infections and infestations	0	3 (0.2)
Appendicitis perforated	0	1 (<0.1)
Cat scratch disease	0	1 (<0.1)
Implant site infection	0	1 (<0.1)
Blood and lymphatic system disorders	0	1 (<0.1)
Lymphadenitis	0	1 (<0.1)

Source: Protocol 2019nCoV-301: 6-Month Booster Safety Addendum to the 12-Month Adolescent Clinical Study Report Table 16, Page 36
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=unique number of participants experiencing the SAE; SOC=system organ class.
1. The data cutoff date for the 6-month Dose 3 safety analysis was 12 November 2022.
Note: If a participant had multiple SAEs within the same SOC/PT, the participant was counted only once at the participant SOC/PT level. Totals for the number of participants at SOC level were not necessarily the sum of those at the PT levels since a participant may have reported 2 or more different SAEs within the higher-level category.

Through 28 days post-Dose 3 of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), 3 SAEs were reported, including the event of cholelithiasis described above, an event of type 2 diabetes mellitus and an event of suicide attempt. These SAEs were assessed by the investigator and sponsor as not related to study vaccine.

Brief details for the 2 additional SAEs are as follows:

- A 12-year-old Black or African American male from the U.S. with a BMI of 33.6 kg/m^2 experienced an SAE of type 2 diabetes mellitus 3 days post-Dose 3. He was hospitalized with positive urine ketones and started treatment with insulin and eventually with metformin. The event was considered resolved and the participant was discharged from the hospital. Treatment with insulin was discontinued and he started with oral metformin. No further information is available as records were unobtainable despite multiple attempts. The Principal Investigator assessed the event of type 2 diabetes as not related to the study vaccine. The Principal Investigator did not provide an alternative etiology for the event of type 2 diabetes mellitus. The Sponsor assessed the event of type 2 diabetes mellitus as not related to the study vaccine.

  Clinical Reviewer Comment: Based on the information provided, the Sponsor's and Principal Investigator's assertion that the type 2 diabetes mellitus was unrelated to vaccine administration is reasonable. The participant was obese (BMI 33.6 kg/m^2) and had a normally functioning pancreas, suggesting that insulin resistance was the underlying cause of the subject's type 2 diabetes mellitus rather than study vaccine administration.

- An 18-year-old Black or African American female from the U.S. with a history of insomnia, anxiety, depression, premenstrual dysphoric disorder, obsessive-compulsive

disorder, and suicidal thoughts experienced an SAE of suicide attempt 9 days post-Dose 3. Concomitant medications included Divalproex ER, APRI, Prozac, and hydroxyzine. The participant attempted suicide by ingesting 240 mg of Prozac and was hospitalized. Treatment included IM Haldol and IM Ativan (both given once) for aggression and combativeness and psychiatric hospitalization. The Principal Investigator assessed the event of suicide attempt as not related to the study vaccine as the event was potentially related to an underlying medical condition. The Sponsor assessed the event of suicide attempt as not related to the study vaccine.

Clinical Reviewer Comment: Although the participant attempted suicide 9 days post-Dose 3 of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), the participant has a significant psychiatric history, including suicidal thoughts. The subjects past medical history and current medications, that include Prozac which has a label warning of increased risk of suicidal thinking, make it unlikely that the study vaccine was related to the suicide attempt.

SAEs were most frequently reported in the MedDRA SOC of *Psychiatric Disorders*. A total of 19 (1.3%) SAEs were reported, including 11 psychiatric SAEs reported by 9 participants (0.6%). The narrative information for the psychiatric events provided in the Protocol 2019nCoV-301: 6-Month Booster Safety Addendum to the 12-Month Adolescent Clinical Study Report was reviewed in detail. In all cases, these participants had a history of psychiatric illness, usually depression, and many were taking selective serotonin reuptake inhibitors, which contain a black box warning for increased suicide risk in pediatric and young adult patients. The time between the last dose of vaccine received and a given psychiatric event ranged from 9 to 178 days. The participant who attempted suicide 9 days after receiving Dose 3 of Novavax COVID-19 Vaccine Adjuvanted (Original Monovalent) is discussed in Section 6.2.3. In all cases, the Investigator and Sponsor considered these events to be unrelated to the study vaccine. Given the psychiatric history of these subjects and lack of temporal association in most of the cases, these psychiatric events are unlikely to be related to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

To comprehensively analyze psychiatric SAEs, a search of the clinical trial safety and post-authorization safety databases for individuals 12 years through 17 years of age using the SMQ for “suicide/self-injury” was performed. In addition, FDA requested that Novavax conduct an observed-to-expected analysis for the cases of suicide/ suicidal ideation/ self-injury observed in adolescents, citing the references to estimate the background rates of suicide/ suicidal ideation/ self-injury in this population. The observed-to-expected analyses that were conducted by Novavax indicate that the SAEs involving suicide attempt, suicidal ideation, and self-injury occurred below the observed background rate for these events in the overall adolescent population.

Clinical Reviewer Comment: Taking all the available evidence into consideration, this reviewer concluded the psychiatric SAEs that occurred in the adolescent study population in Study 301 do not constitute a safety signal.

The narrative information for non-psychiatric SAEs was also reviewed. In all cases, the Investigator and Sponsor considered the events to be unrelated to the study vaccine.

Clinical Reviewer Comment: Based on the clinical information provided, the nature of the events (trauma, accidents) does not provide a biologically plausible explanation for potential causality. In addition, other SAEs (e.g., pancreatitis, cholelithiasis, and lymphadenopathy)

that could have potential biological plausibility presented clear alternative explanations and lack of close temporal association that make a causality association with the vaccine unlikely.

Medically Attended Adverse Events
Less than 5% of adolescent participants reported MAAEs. MAAEs were most frequently reported in the MedDRA SOC *Infections and Infestations*. Within this SOC, upper respiratory tract infection was the most frequent (≥0.3% of participants) MAAE reported.

Adverse Events of Special Interest
There were no AESIs of PIMMCs reported during the Dose 3 safety follow-up period.

Adverse Events Resulting in Study Discontinuation
One (<0.1%) adolescent participant reported an AE, leading to study discontinuation (anxiety) during the Dose 3 safety follow-up period. This event was serious and assessed as not related to study vaccine by both the Principal Investigator and Sponsor; the participant had an ongoing medical history of anxiety.

Deaths
There were no deaths reported.

Subgroup Analyses
No imbalances were noted with regard to age, sex, race, and ethnicity for solicited, unsolicited, serious, and treatment-related MAAEs.

Summary and Conclusions
Based on the safety review of the 1499 participants in this extended follow up period, no new safety signals have been identified.

6.2.3.5 Summary of Findings for Study 301 Pediatric Extension

Effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine based on comparisons of GMTR and SCR 28 days after a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine with neutralizing antibody response 14 days after a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously not vaccinated, was inferred from immunogenicity data from Study 301 Pediatric Extension, which met all pre-specified noninferiority success criteria. Formal immunobridging analyses utilizing neutralizing antibody responses after a 2-dose series were previously used to infer effectiveness of Novavax COVID-19 Vaccine (Original monovalent) in this age group; therefore, it is reasonable to further infer effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine based on demonstrated noninferiority of immune responses following the second and third doses.

Data from Study 301 Pediatric Extension support the safety of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) when administered as a single-dose regimen to previously vaccinated individuals 12 years through 17 years of age. No new safety signals or related SAEs were identified. The proportions of participants reporting each solicited AR (except fever) and

the proportions of participants reporting Grade 3 severity for each solicited AR increased after the 3rd dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), when compared to both the first and second doses. This pattern of increasing reactogenicity following successive doses of vaccine was also observed following the 2-dose series in both individuals 18 years of age and older and individuals 12 years through 17 years of age and following a booster dose in individual 18 years of age and older. A total of 40.5% of participants reported any Grade 3 event following the 3rd dose of vaccine; Grade 3 events were most frequently reported for solicited ARs of fatigue/malaise, myalgia, and headache. While contemporaneous comparisons of solicited ARs between individuals 18 years of age and older and individuals 12 years through 17 years of age are not available, the proportions of participants 12 years through 18 years of age reporting solicited severe ARs after the 3rd dose is generally higher than that previously reported for participants 18 years of age and older. This pattern was also observed following Dose 2 of the vaccine. In summary, solicited ARs were commonly reported in participants 12 years through 17 years of age, with a high proportion of participants 12 through 17 years of age reporting severe reactions. 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 Fact Sheets.

6.2.4 Summary of Vaccine Effectiveness and Safety

Effectiveness

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older not previously vaccinated with a COVID-19 vaccine and the effectiveness of a single-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 18 years of age and older previously vaccinated with a COVID-19 vaccine is inferred from immunogenicity data from Study 311 Parts 1 and 2 as follows:

- Based on superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by monovalent vaccines (Omicron BA.5) and monovalent vaccine (Omicron BA.1), each compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), it is reasonable to expect that in individuals 18 years of age and older that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).
- Additional supportive immunogenicity data from Study 311 Part 2 includes: (1) noninferior neutralizing antibody responses induced by the monovalent vaccine (Omicron BA.5) compared to the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against the ancestral (Wuhan) strain, the virus upon which the currently authorized formulation was based, and (2) superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by the bivalent vaccine (Original and Omicron BA.5) compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), demonstrating that multiple modified vaccines using a similar manufacturing process and the same antigen and adjuvant dose can induce a superior neutralizing antibody response to an Omicron sublineage compared the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

Effectiveness of a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age not previously vaccinated with a

COVID-19 vaccine is extrapolated from immunogenicity data from Study 311 Parts 1 and 2 support as follows:

- The superior neutralizing antibody responses (as measured by GMTR) and noninferior SRRs induced by the monovalent vaccine (Omicron BA.5), the monovalent vaccine (Omicron BA.1) and bivalent (Original and Omicron BA.5), each compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), can be extrapolated to adolescents in the context of previously reviewed comparable efficacy and immunogenicity results between individuals 18 years of age and older and individuals 12 years through 17 years of age observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum). Therefore, for individuals 12 years through 17 years of age, it is reasonable to expect that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

Effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine is extrapolated from immunogenicity data from Study 311 Parts 1 and 2 and Study 301 Pediatric Extension as follows:

- Single-dose regimen: Immunogenicity data from Study 301 Pediatric Extension supports the effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine based on comparisons of GMTR and SCR 28 days after a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine with neutralizing antibody response 14 days after a 2-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously not vaccinated, which met all pre-specified noninferiority success criteria. Formal immunobridging analyses using neutralizing antibody responses after a 2-dose series were previously used to infer effectiveness of Novavax COVID-19 Vaccine (Original monovalent) in this age group; therefore, it is reasonable to further infer effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in individuals 12 years through 17 years of age previously vaccinated with a COVID-19 vaccine based on demonstrated noninferiority of immune responses following the second and third doses.
- 2023-2024 Formula (strain change): The superior neutralizing antibody responses (as measured by GMTR) and non-inferior SRRs induced by the monovalent vaccine (Omicron BA.5), the monovalent vaccine (Omicron BA.1) and bivalent (Original and Omicron BA.5), each compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), can be extrapolated to individuals 12 years through 17 years of age in the context of previously reviewed comparable efficacy and immunogenicity results between individuals 18 years of age and older and individuals 12 years through 17 years of age observed after a 2-dose series of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum). Therefore, for individuals 12 years through 17 years of age, it is reasonable to expect that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), manufactured using a similar process and the same antigen and adjuvant dose, will result in increased immune

responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages, when compared with Novavax COVID-19 Vaccine Adjuvanted (Original monovalent).

Safety

The total safety database for all Novavax COVID-19 vaccine, adjuvanted includes approximately 45,000 participants who received at least one dose of vaccine at the authorized dose level. Approximately 28,500 individuals received at least one dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), approximately 1,000 individuals received at least one dose of monovalent or bivalent vaccine containing spike proteins of SARS-CoV-2 Omicron variants, and approximately 15,000 individuals received at least one dose of a formulation of the original monovalent vaccine that was manufactured using a different manufacturing process.

Data from Study 311 Parts 1 and 2 support the safety of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) strain change for all age groups and regimens because these vaccines are manufactured using a similar process. The four formulations tested in adults in Study 311 (monovalent vaccine [Omicron BA.5], monovalent vaccine [Omicron BA.1], bivalent vaccine [Original and Omicron BA.5], and bivalent vaccine [Original and Omicron BA.1]) were well tolerated with an acceptable safety profile when administered as a single-dose regimen in previously COVID-19 vaccinated adult participants. 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).[40,41] Two related SAEs of oculomotor cranial nerve palsy were reported in close temporal relationship to vaccination with bivalent vaccine (Original and Omicron BA.5) and monovalent vaccine (Omicron BA.5). In addition to inclusion of these events in product labeling (see Fact Sheet), 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)” as an Important Potential Risk in the pharmacovigilance plan and enhanced surveillance in postmarketing (see Section 7.5). No other new safety concerns were identified. Although there are no clinical safety data for the modified vaccine formulations in adolescents, it is reasonable to expect a similar safety profile between adults and adolescents for Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), as (1) the safety profiles for the modified vaccines were comparable to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in Study 311 Part 1 and 2, and (2) the general safety profile for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) has been comparable between individuals 18 years of age and older and individuals 12 years through 17 years of age based on the available clinical data.

Data from Study 301 Pediatric Extension support the safety of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) when administered as a single-dose to previously vaccinated adolescents. No new safety signals or related SAEs were identified. Information on the high proportion of adolescents reporting severe solicited reactions will be communicated in the Fact Sheets.

6.3 Immunocompromised Individuals

Solid organ transplant patients are immunosuppressed due to the effects of immunosuppressive medications administered to prevent organ rejection, such as cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, and anti-thymocyte globulin, which result in interference with cellular and humoral immune responses. These and other immunosuppressive medications are used in a variety of conditions to address immune dysregulation, resulting in similar interference with cellular and humoral immune responses. Thus, individuals receiving these

medications to prevent rejection of solid organ transplant or for the treatment of immune dysregulation likely have an attenuated response to the administration of vaccines to prevent COVID-19.

Effectiveness and safety of additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for individuals 12 years of age and older with certain kinds of immuno-compromise[a] is inferred from the following evidence that additional doses of Novavax COVID-19 Vaccine, Adjuvanted are immunogenic and well-tolerated following previous COVID-19 vaccines (for detailed review of the evidence, please refer to Section 6.4.1 and Section 7.1 of the Decision Memorandum). Based on these data, it is reasonable to expect that additional doses administered to individuals 12 years of age and older with certain kinds of immunocompromise will provide additional protection against COVID-19.

- Following previous doses of Novavax COVID-19 Vaccine, Adjuvanted: Immunogenicity of a 3rd dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in immunocompetent individuals previously vaccinated with two-dose series of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in adolescents 12 years through 17 years of age (see Section 6.2.3) and in adults 18 years of age and older (see Section 6.4.1 of the Decision Memorandum).
- Following previous doses of an mRNA COVID-19 Vaccine: Data from administration of an additional dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Section 7.1 of the Decision Memorandum), monovalent vaccine (Omicron BA.1), monovalent vaccine (Omicron BA.5), bivalent vaccine (Original and Omicron BA.4/BA.5) (see Sections 6.2.1.3 and 6.2.2.3 above) in immunocompetent individuals 18 years of age and older who previously received two or three doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Moderna COVID-19 Vaccine (Original monovalent).

6.4 Postmarketing Safety

Review of postmarketing safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) indicate a safety profile that is comparable to that of the clinical safety data submitted and reviewed for the initial Emergency Use Authorization.

Although vaccine administration data are not available or updated for all countries/jurisdictions, according to the Sponsor's monthly SSR #20, as of August 31, 2023, at least 2,906,669 doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had been administered and approximately 103,477,920 doses had been distributed worldwide. Although the CDC stopped reporting COVID-19 vaccine administration data in May 2023, according to their last update on May 10, 2023, 89,195 doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had been administered in the U.S.[43] According to the CDC, as of August 9, 2023, 1,507,500 doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had been distributed in the U.S.[44]

In recipients of all doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) among individuals 12 years of age and older, the most frequently reported PTs in the VAERS were dizziness, headache, fatigue, chest pain, dyspnea, pain, nausea, pyrexia, myalgia, and paraesthesia. For important risks identified in the pharmacovigilance plan for Novavax COVID-

[a] Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

19 Vaccine, Adjuvanted (Original monovalent), anaphylaxis and myocarditis/pericarditis are identified risks that are included in the EUA Fact Sheets. The Sponsor is conducting a safety-related post-authorization study for Novavax COVID-19 Vaccine, Adjuvanted, to evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to Section 7 for details).

Taken together, these data informed FDA's assessment of the known and potential benefits and risks of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Based upon the accumulated experience with all doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) to date, FDA determined that it was reasonable to conclude that the available safety data support a favorable benefit-risk profile for use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) and the proposed updated vaccination schedule.

7 FDA Review of Other Information Submitted in Support of the EUA Amendment

7.1 Chemistry Manufacturing and Controls (CMC) Information:

The Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is manufactured using the same baculovirus/Sf-9 insect cell platform as the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). The Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) contains a recombinant full-length spike glycoprotein (rS) of the Omicron XBB.1.5 sublineage of SARS-CoV-2. The XBB.1.5 rS is expressed from a recombinant baculovirus vector in *Spodoptera frugiperda* (Sf9) insect cells, purified by (b) (4) chromatography and formulated in a buffer containing sodium phosphate, sodium chloride, and polysorbate 80. The drug product (DP) is a co-formulation of the XBB.1.5 rS drug substance (DS) with a saponin-based Matrix-M adjuvant derived from the soapbark tree (*Quillaja saponaria* Molina) and formed into matrix particles with phosphatidylcholine and cholesterol.

Both the rS DS and the DP of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) for supply to the U.S. under EUA 28237/0 were authorized to be manufactured at the site, the Serum Institute of India, Private Limited. The request for authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is also supported with manufacturing information (for both rS DS and DP) from the same site. The rS DS is manufactured at (b) (4) scales. The rS DS manufacturing process is similar between the Original monovalent [ancestral (Wuhan)] and the 2023-2024 Formula (Omicron XBB.1.5) . Data from a comprehensive analytical comparability assessment of the Original monovalent [ancestral (Wuhan)] and 2023-2024 Formula (Omicron XBB.1.5) rS DS lots, manufactured at the (b) (4)-scale, support comparable product quality.

There have been no major changes to the CMC information for the Matrix-A and Matrix-C adjuvant components authorized under the original EUA. The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) DP is authorized for formulation at (b) (4) scale and filling into 10-dose multidose vials as well as formulation at (b) (4) scale and filling into 5-dose multidose vials. The Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is manufactured using the validated (b) (4)-scale process and filled as 5-dose multidose vials in the same container closure system authorized for the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) DP. The validated (b) (4) manufacturing process was verified for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) with the manufacture of 3 commercial DP lots. A comprehensive analytical comparability assessment has been performed and the data support quality comparability of the Novavax COVID-19 Vaccine, Adjuvanted

(Original monovalent) and the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) by the (b) (4) DP process. The Sponsor will submit the Certificates of Analysis of DP lots to be distributed under the EUA for review, at least 48 hours prior to lot distribution in the U.S.

Stability studies have been designed to support the use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) under the EUA. The rS DS for the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) has an authorized shelf-life of (b) (4) based on real-time stability data of up to (b) (4) .

The shelf life for storage of Original monovalent [ancestral (Wuhan)] rS DS at (b) (4) is (b) (4) . Based on the similarity in the manufacturing process, composition (excipients), storage temperature (b) (4) , and comparable analytical quality of the Original monovalent [ancestral (Wuhan)] and 2023-2024 Formula (Omicron XBB.1.5) rS DS, and the stability data supporting the storage of Original monovalent [ancestral (Wuhan)] rS DS at (b) (4) for (b) (4) , the proposed initial (b) (4) shelf life for storage of the 2023-2024 Formula (Omicron XBB.1.5) rS DS at (b) (4) is deemed appropriate. The shelf-life can be further extended with real-time data when available.

The shelf life for storage of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) DP at 2-8°C is 9 months. Based on the similarity in the manufacturing process, composition (excipients), storage temperature (2-8°C), and comparable analytical quality of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DP, and the stability data supporting the storage of Novavax COVID-19 Vaccine (Original monovalent) DP at 2-8° for 9 months and 3 months of potency data for development lots of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) the proposed initial 9-month shelf-life for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DP at 2-8°C is also deemed appropriate.

All stability studies of the DS and DP lots are ongoing and stability data will be submitted to the EUA as they become available.

The analytical methods for the assessment of critical quality attributes (identity, purity, quality, and potency) of the DS and DP for product release and stability evaluation have been qualified/validated for performance and met pre-specified acceptance criteria for accuracy, inter- and intra-assay precision, specificity, and sensitivity, and are suitable for their intended use. The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was authorized with the use of the (b) (4) assay in measuring the total protein concentration of the DP. The Sponsor observed high variability in the protein content measured and the assay did not meet accuracy and system suitability criteria when used in the testing of monovalent vaccine (Omicron BA.5) DP. A (b) (4) in which (b) (4) DP sample, was developed and validated for measuring the rS content in the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). A preliminary bridging of the (b) (4) method with the (b) (4) assay using developmental lots of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) DP shows that the rS content measured by (b) (4) correlates with the (b) (4) measured by (b) (4) . The specification for rS concentration for DP release and stability evaluation by (b) (4) . This specification is acceptable.

The Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was authorized with the use of (b) (4) for identity testing of the rS DS and DP. Due to the unavailability of

specific antibody reagents for the XBB.1.5 spike protein, identity testing is performed using a validated (b) (4) method in which a test sample is (b) (4) . The (b) (4) are identified by (b) (4) , with (b) (4) sequence coverage. An XBB.1.5 monoclonal antibody has also been developed and characterized for use in (b) (4) . A (b) (4) assay for testing the identity of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) has been developed and validated.

Regarding the evaluation of relative potency with a heterologous reference standard (Wuhan rS), an interim specification of (b) (4) is authorized for the release and stability monitoring of the 2023-2024 Formula (Omicron XBB.1.5) rS DS. For the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), an interim specification range of (b) (4) is authorized for DP release and a range of (b) (4) is authorized for stability monitoring, considering the estimated monthly degradation rate of the DP under long-term storage. The relative potency of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) will be tested within (b) (4) days post-manufacture. These specification ranges for the 2023-2024 Formula (Omicron XBB.1.5) rS DS and DP are preliminary and the Sponsor will re-evaluate them as more data become available or when a qualified homologous (XBB.1.5 rS) reference standard becomes available.

7.2 Facilities

The manufacture of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is performed at existing facilities that were previously included in the EUA for the manufacture of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). These facilities are included in the EUA request for the manufacture of the authorized 5 µg/dose of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). Two release testing facilities were removed from the original EUA (Original monovalent) and a new release test facility was introduced. No additional changes were made to the facilities, equipment, container closure systems, quality systems and controls. FDA finds that all facilities within the scope of this authorization for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) are adequate to support the use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) under an EUA.

7.3 Nonclinical Studies

The Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) was evaluated in three studies in mice, as well as in an ongoing study in non-human primates. The rS antigen drug substance lots used in the nonclinical studies were manufactured at small scales and were (b) (4) (5 µg and 50 µg Matrix-M per dose in mice and macaques, respectively). Animals were inoculated by the intramuscular route, the authorized route of administration of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). In one study, two formulations of rS antigen containing 0.1 µg or 1 µg of the original [ancestral (Wuhan)] rS, Omicron BA.2 rS, or Omicron XBB.1.5 rS, each mixed with 5 µg of Matrix-M adjuvant, were inoculated into naïve mice on a prime/boost schedule at an interval of 2 weeks. In serum samples obtained 7 days after the second dose, the levels of antibody responses (total IgG, ACE2-binding inhibition, and pseudovirus neutralization) against the original rS and Omicron rS variants (BA.1, BA.2, BA.5, BQ.1.1, XBB.1.5, CH.1.1, and XBB.1.16) were dose-dependent, with the highest antibody responses induced against homologous rS. Serum samples from the group vaccinated with Omicron XBB.1.5 (1 µg rS) neutralized pseudotype viruses of Omicron sublineages (BA.2, BA.5, BQ.1.1, XBB.1.5, CH.1.1 and XBB.1.16), with the highest neutralizing titers against XBB.1.5 and XBB.1.16. In the second

study in mice, naïve animals received a prime/boost vaccination with 1 µg of rS of the original, or Omicron BA.2, BA.5, XBB.1.5, or a bivalent formulation (0.5 µg original rS + 0.5 µg XBB.1.5 rS, with 5 µg Matrix-M). Serum samples obtained 1 week after the second dose had a similar pattern of antibody response as above, with higher titers of antibodies against homologous rS. Serum samples from the XBB.1.5 rS vaccination groups neutralized pseudotype viruses of Omicron subvariants (BA.2, BA.5, BQ.1.1, CH.1.1, XBB.1.5, XBB.1.16, and XBB.2.3), with the highest titers recorded against XBB.1.5 and XBB.1.16 pseudotype viruses. Serum samples from the group vaccinated with the original rS had high neutralizing antibodies against the homologous (original) pseudotype virus but not against most Omicron pseudotype viruses (including XBB.1.5 rS). The bivalent formulation had neutralizing activity against the original and all Omicron pseudotype viruses, but the monovalent Omicron XBB.1.5 rS induced stronger neutralizing antibody titers against Omicron XBB.1.5, XBB.1.16, and XBB.2.3 pseudoviruses than the bivalent formulation.

To evaluate the effect of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in previously vaccinated mice, naïve mice were vaccinated with a 2-dose series of the original rS (100 mice) or a bivalent formulation (0.5 µg original rS + 0.5 µg BA.5 rS, with 5 µg Matrix-M [100 mice]) at a dosing interval of 2 weeks. At 33 days after Dose 2, mice were assigned into groups-of-10 and administered a single-dose regimen (Dose 3) of adjuvanted monovalent original rS, or monovalent Omicron BA.5 rS, XBB.1.5 rS, BQ.1.1 rS, CH.1.1 rS, and XBB.1.16 rS, or adjuvanted bivalent formulations (original rS + BA.5 rS; original rS + XBB.1.5 rS; original rS + BQ.1.1 rS; or original rS + XBB.1.16 rS). Neutralizing antibody titers against the original and all Omicron pseudotype viruses (BA.5, BQ.1.1, CH.1.1, XBB.1.5, XBB.1.16. and XBB.2.3) were significantly higher 2 weeks after Dose 3 in the groups initially vaccinated with bivalent original rS/BA.5 rS followed by a single-dose regimen of monovalent XBB.1.5 or bivalent original rS/XBB.1.5 rS. Cell-mediated immune response was evaluated in two of the mouse studies. Inoculation of XBB.1.5 rS induced cell-mediated immune responses, including comparable levels of CD4 T cells expressing Th1 ($IFN\gamma^+$, $IL\text{-}2^+$ and $TNF\text{-}\alpha^+$) and Th2 ($IL4^+$) cytokines, as well as $IFN\gamma^+$, $IL\text{-}2^+$ and $TNF\text{-}\alpha^+$ CD8 T cells.

In an ongoing immunogenicity study in non-human primates, rhesus macaques were vaccinated with a 2-dose series at an interval of 3 weeks, using adjuvanted monovalent original rS or BA.5 rS (5 µg + 50 µg Matrix-M), or a bivalent formulation (2.5 µg original rS + 2.5 µg BA.5 rS, with 50 µg Matrix-M). Preliminary data from this study show the detection of cross-neutralizing antibodies against Original and Omicron (BA.2, BA.5, BQ.1.1, CH.1.1, XBB.1.5, XBB.1.16, and XBB.2.3) pseudotype viruses in macaques 2 weeks after the inoculation of a single-dose regimen (Dose 3) of monovalent Omicron XBB.1.5 + 50µg Matrix M1 adjuvant, 225 days after the completion of the 2-dose series in previously unvaccinated non-human primates. When peripheral blood mononuclear cells obtained 2 weeks after the single-dose regimen (Dose 3) were re-stimulated *in vitro* with the original rS, or Omicron BA.5 rS, XBB.1.5 rS or XBB.1.16 rS, rS-specific $IFN\gamma^+$, $IL\text{-}2^+$ and $TNF\text{-}\alpha^+$, and polyfunctional ($IFN\gamma^+/IL\text{-}2^+/TNF\text{-}\alpha^+$) Th1 CD4 T cells were detected, irrespective of the stimulating rS. Taken together, data from these nonclinical studies indicate that the adjuvanted Omicron XBB.1.5 rS induces antibody responses, including neutralizing antibodies, as well as cell-mediated immune responses when inoculated into naïve mice, or as a booster in mice and macaques. Data from the non-clinical studies are supportive of the request for authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula).

7.4 Inspection of Clinical Study Sites

The review team decided that Bioresearch Monitoring inspections are not needed to support the review of this EUA amendment.

7.5 Pharmacovigilance Activities

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., cranial nerve disorders affecting cranial nerves III, IV, or VI)
- 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 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)" as an Important Potential Risk in the PVP. 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.

7.5.1 Sponsor Pharmacovigilance Activities

The Sponsor will conduct both passive and active surveillance to monitor the post-authorization safety for the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); myocarditis; pericarditis; Multisystem Inflammatory Syndrome; COVID-19 resulting in hospitalization or death. In addition, FDA requested that Novavax submit all reports of "Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)" (regardless of seriousness) to VAERS within 15 days of receipt.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether associated with an AE; newly identified safety concerns; and cumulative and interval doses distributed. The EUA Letter of Authorization will be revised from a required monthly submission of periodic safety reports to submission monthly or at another appropriate reporting interval determined by the Office of Biostatistics and Pharmacovigilance to provide flexibility to modify the reporting interval, if appropriate, based on the continued accumulation of postmarketing safety data on Novavax's COVID-19 vaccines. In addition, FDA requested that Novavax perform aggregate review and analysis of postmarketing cases (interval and cumulative) of "Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)" in each subsequent

periodic safety report.

- Post-authorization observational studies will evaluate the association between Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and cases of COVID-19 resulting in hospitalization. The studies below are being conducted for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in large-scale databases and will include a sub-analysis for Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in authorized age groups in the following studies:
    - **Study 2019nCoV-405**: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)
    - Objective: To estimate the risk of obstetric outcomes, neonatal outcomes, and infant outcomes among pregnant women 18 years of age and older exposed to single (homologous) or mixed (heterologous) Novavax COVID-19 vaccine series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccines during pregnancy.
    - **Study 2019nCoV-404**: U.S. Post-authorization safety study using a claims and/or electronic health records database
    - Objective: To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted in individuals 12 years of age and older in the U.S. using a self-controlled case series (SCCS) design.
    - **Study 2019nCoV-402**: UK Post-Authorization Safety Study Using the Clinical Practice Research Datalink
    - Objective: To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine, Adjuvanted in individuals 12 years of age and older in England using a self-controlled case series (SCCS) design (i) a SCCS design and (ii) a comparative cohort design.

Additionally, the Sponsor is conducting the following effectiveness studies:

- **Study 2019nCoV-403**: U.S. Post-Authorization Effectiveness Study Using a Claims and/or electronic health records database
- Objective: To estimate the effectiveness of the Novavax COVID-19 Vaccine in preventing COVID-19 hospitalizations compared to unvaccinated individuals.
- **Study 2019nCoV-401**: EU/EEA Post-Authorization Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform
- Objective: To estimate vaccine effectiveness of Novavax COVID-19 Vaccine against hospitalization due to laboratory-confirmed SARS-CoV-2 in patients with severe acute respiratory infection.

FDA requested that Novavax add “Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)” as a safety outcome in their ongoing post-authorization safety studies.

Other Pharmacovigilance Activities

Mandatory reporting by vaccination providers to VAERS, and to the extent feasible, to the Sponsor, for the following events:

- Vaccine administration errors whether or not associated with an AE
- Serious AEs (irrespective of attribution to vaccination)
- Myocarditis
- Pericarditis
- Cases of multisystem inflammatory syndrome
- Cases of COVID-19 that result in hospitalization or death

7.6 EUA Prescribing Information and Fact Sheets

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), and Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

8 Benefit-Risk in the Context of the Proposed EUA for Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in Individuals 12 years of Age and Older

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2, and the virus has been responsible for over 104 million cases of COVID-19 and over 1.1 million deaths in the U.S. Since the start of the pandemic, there has been a succession of SARS-CoV-2 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and other Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. In general, these interventions are most effective in disease of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA-approved and -authorized vaccines may provide protection to individuals against COVID-19 and play an important role in reducing the societal and economic disruption caused by the COVID-19 pandemic. Currently approved COVID-19 vaccines for disease prevention in individuals 12 years of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech (2023-2024 Formula). In addition, there is an adjuvanted, protein subunit vaccine, Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), authorized for use in individuals 12 years of age and older.

The original monovalent vaccines were based on the original (ancestral) strain of SARS-CoV-2, and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. Vaccine effectiveness against symptomatic disease declined more rapidly than that against serious disease, as illustrated by studies conducted in the U.S.,[45,46] Israel,[35] Qatar,[32] Portugal,[47] and England.[27] In the setting of the viral variants that have emerged in the past, booster doses with available vaccines (based on the ancestral strain) were able to restore some degree of protection against serious and symptomatic disease.

Bivalent COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage compared with the original

monovalent COVID-19 vaccines. However, the effectiveness of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines against Omicron sublineages, including the most recently circulating sublineages, appears to wane over time (refer to Section 3.1), suggesting that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted.

Approximately 45,000 participants in the total safety database have received at least one dose of any Novavax COVID-19 Vaccine, Adjuvanted, at the authorized dose level (refer to Section 6.2.4). The safety and effectiveness data accrued with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.1), monovalent vaccine (Omicron BA.5), and bivalent vaccine (Original and Omicron BA.5) are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), are relevant because all these vaccines are manufactured using a similar process, and all use the same antigen and adjuvant dose. Evidence to support the safety and effectiveness of a 2-dose regimen of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age or older not previously vaccinated with a COVID-19 vaccine, and evidence for safety and effectiveness of a single-dose regimen of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older previously vaccinated is discussed in Section 6.2.3.

In addition, the nonclinical data reviewed indicate that Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), when administered to vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) against currently circulating XBB-related sublineages. Based on the totality of the available evidence (reviewed in detail in sections 6 and 7), it is reasonable to expect in individuals 12 years of age and older that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) will likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the currently predominant Omicron sublineages, compared to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).

Adverse reactions reported in clinical trials following administration of the Novavax COVID-19 Vaccine, Adjuvanted include injection site pain/tenderness, fatigue/malaise, muscle pain, headache, joint pain, nausea/vomiting, injection site redness, injection site swelling, fever, chills, injection site pruritus, hypersensitivity reactions, lymphadenopathy-related reactions, myocarditis, and pericarditis. Myocarditis, pericarditis, anaphylaxis, paresthesia, and hypoesthesia have been reported following administration of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) outside of clinical trials. Overall, the safety data accrued with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) because both vaccines are manufactured using a similar process. Given the concerns outlined in this memorandum regarding the two clinical trial cases of ocular motor cranial nerve palsies 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)” as an Important Potential Risk in the PVP. There were no other safety signals identified in the submitted safety data that are not already addressed in Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) (see Decision Memorandum). Post-deployment monitoring for adverse events using both passive and active surveillance systems will be used to assess whether any new safety concerns emerge.

8.1.1 Uncertain Benefits/Data Gaps

Effectiveness of an updated strain against SARS-CoV-2 variants of concern
As summarized above, 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 (2023-2024 Formula) because all these vaccines are manufactured using a similar process, and all used the same antigen and adjuvant dose. It is reasonable to expect from the totality of the available evidence that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) will likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the currently predominant Omicron sublineages, compared to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent). However, data are lacking to directly demonstrate clinical efficacy of the 2023-2024 formula vaccine against clinical disease outcomes from SARS-CoV-2 Omicron subvariant infection. Furthermore, other subvariants could emerge in the future, against which the 2023-2024 formula vaccine may be less effective.

Single-dose regimen durability of protection
Based on the 28-day post-Dose 3 immunogenicity data submitted for review, there are insufficient available data to assess sustained effectiveness.

Effectiveness of vaccination with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) against long term effects of COVID-19 disease
Prevention of cases of symptomatic COVID-19 will likely result in prevention of some COVID-19 cases with long-term sequelae; however, there are insufficient data available to verify this potential benefit.

Future effectiveness of vaccination as influenced by characteristics of the disease epidemiology, changes in the virus, and/or potential effects of coinfections
The ongoing and uncertain evolution of the disease and its effect on the population, such as increased or decreased 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 (2023-2024 Formula) or other COVID-19 vaccines. Ongoing evaluation of vaccine effectiveness following issuance of the EUA is critical to address these uncertainties.

8.1.2 Known and Potential Risks

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.

8.1.3 Uncertain Risks/Data Gaps

Adverse reactions that are very 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

(2023-2024 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., cranial nerve disorders 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 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 during the post-authorization period to detect any new safety signals.

Safety of a dose 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 12 years of age, pregnant or lactating individuals, or in individuals with certain kinds of immunocompromise (see Section 8 Use in Specific Populations of the Fact Sheet). For pregnant or lactating individuals, available safety data from use of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in non-pregnant, non-lactating individuals do not raise specific safety concerns for the safety of future use in pregnant or lactating individuals. However, as noted above, according to CDC as of May 2023 less than 90 thousand doses of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) had been administered (outside of clinical studies) in the U.S.

Table 33. Summary of Benefit-Risk Assessment

Dimension	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. • There has been a succession of SARS-CoV-2 variants (Delta, Omicron BA.1, BA.5. and more recently XBB.1.5, among others) that have led to a reduction in COVID-19 vaccine effectiveness. • SARS-CoV-2 XBB-lineage viruses currently predominate in the U.S. • Although previously administered bivalent mRNA COVID-19 vaccines continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased.	• 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 those individuals. • Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and Original monovalent mRNA-based COVID-19 vaccines authorized in the U.S. initially had high effectiveness (90-95%) against symptomatic disease; however, in combination with waning individual immunity, vaccine effectiveness declined with the emergence of the now dominant Omicron variant; this effect is most prominently observed in older individuals; decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Options for treatment or prevention of COVID-19	• Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity. • Currently, the 2023-2024 Formula of the mRNA COVID-19 vaccines are available for use in the U.S. for individuals 6 months and older. • An adjuvanted, protein subunit COVID-19 vaccine (Original monovalent) is authorized for use as a primary series in individuals 12 years of age and older and as a single booster dose for certain individuals 18 years of age and older.	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID). • COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19.
Benefit	• Preclinical data demonstrating that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), when used in vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies against circulating XBB-related sublineages compared to Novavax COVID-19 Vaccine (Original monovalent). • 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 (2023-2024 Formula) may provide benefit, particularly against circulating XBB 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 (2023-2024 Formula) compared with the currently authorized Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) it is reasonable to expect that administration of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) doses may provide additional benefit compared with administration of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent)
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 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) (important potential risk)	• Post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge.

8.2 Conclusions Regarding Benefit-Risk

For individuals 12 years of age and older, the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) outweigh the known and potential risks of the vaccine, when used as described in Fact Sheet for Healthcare Providers Administering Vaccine, considering the totality of available evidence and the outstanding uncertainties. During the current wave of COVID-19 caused in large part by the XBB-related sublineages, administration of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) is expected to have a favorable benefit-risk profile, restoring protection against serious outcomes from COVID-19.

Although mRNA COVID-19 vaccines are available, there may be individuals for whom the mRNA vaccines are not accessible or clinically appropriate. Additional preventative options are needed that provide greater flexibility in meeting the needs of potential vaccinees. Authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) will provide an alternative for these individuals.

9 Overall Summary and Recommendations

Given the VRBPAC recommendations from the June 15, 2023, meeting and following review of the EUA request, the review team considered the following in its assessment of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula):

- As summarized in Section 2 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- The scientific evidence available to support this EUA request includes the following:
    - Preclinical data demonstrating that Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) when used in vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies against XBB-related sublineages compared to Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent),
    - Chemistry, Manufacturing and Control Information related to multi-dose vial presentations of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), including the manufacturing facilities,
    - Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated a 2-dose series in individuals 12 years of age and older previously not vaccinated with a COVID-19 vaccine and single-dose regimen with the Novavax COVID-19 Vaccine, Adjuvanted (including Original monovalent and four modified Novavax COVID-19, Vaccine, Adjuvanted formulations containing Omicron sublineage components) in individuals 12 years of age and older previously vaccinated with a COVID-19 vaccine, and
    - Postmarketing safety surveillance data of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).
- Although available evidence suggests that the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) continues to provide protection against serious disease from COVID-19 in the U.S., based on the totality of available scientific evidence, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), administered as a single-dose regimen to previously vaccinated individuals 12 years of age

and older at least 2 months after the last previous dose of any monovalent (original) and/or bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccine, and administered as 2-dose series, three weeks apart, to individuals 12 years of age and older not previously vaccinated with any COVID-19 vaccine, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.

- Based on the totality of available scientific evidence, in previously unvaccinated individuals 12 years of age and older, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), administered as 2-dose series may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.
- Based on the totality of available scientific evidence, in individuals 12 years of age and older who have already received one or more doses of a monovalent original and/or bivalent COVID-19 vaccine, it is reasonable to conclude that the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), administered as a single-dose regimen, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.
- Based on the totality of available scientific evidence, it is reasonable to conclude that administration of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older with certain kinds of immunocompromise may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages, as described below:
    - an additional dose of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula)
    - additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances, with the timing of the additional doses may be based on the individual's clinical circumstances.
- As summarized in Section 6, safety and effectiveness of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in individuals 12 years of age and older is supported by clinical studies of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.1), monovalent vaccine (Omicron BA.5), and bivalent vaccine (Original and Omicron BA.5) and postmarketing safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent).
- Based on FDA's review of the available scientific evidence, including the data summarized in Section 7 and assessment of benefits and risks in Section 8 of this review, the known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) outweigh the known and potential risks when used in an appropriate schedule based on previous vaccination status for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.
- Known and potential benefits of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to XBB-related sublineages.
- Uncertainties include those around the level of effectiveness against future SARS-CoV-2

variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations, such as severely immunocompromised individuals.

- Known and potential risks include generally self-limited common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, and axillary swelling/tenderness) and rarely anaphylaxis and myocarditis/pericarditis based on experience in Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) recipients. The risk of ocular motor cranial nerve disorders (i.e., cranial nerve disorders 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. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis, Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI) and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

Based on the considerations outlined above, the review team recommends: 1) removing authorization for emergency use of the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the U.S.; and 2) revision of the EUA to provide for use of the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) administered in an appropriate schedule based on previous vaccination status, as reflected in the Fact Sheets.

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11 Appendices

11.1 Appendix A. Adverse Events of Special Interest

Table 34. Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	CDC Definition
Probable Acute Myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms[1]: Chest pain, pressure, or discomfort Dyspnea, shortness of breath, or pain with breathing Palpitations Syncope AND ≥1 new finding of Troponin level above upper limit of normal (any type of troponin) Abnormal ECG or rhythm monitoring findings consistent with myocarditis[2] Abnormal cardiac function or wall motion abnormalities on echocardiogram cMRI findings consistent with myocarditis [3] AND No other identifiable cause of the symptoms and findings
Confirmed Acute Myocarditis	Presence of ≥1 new or worsening of the following clinical symptoms[1]: Chest pain, pressure, or discomfort Dyspnea, shortness of breath, or pain with breathing Palpitations Syncope AND ≥1 new finding of Histopathologic confirmation of myocarditis[4] cMRI findings consistent with myocarditis[3] in the presence of troponin level above upper limit of normal (any type of troponin) AND No other identifiable cause of the symptoms and findings
Acute pericarditis[5]	Presence of ≥2 new or worsening of the following clinical features: Acute chest pain [6] Pericardial rub on exam New ST-elevation or PR-depression on ECG New or worsening pericardial effusion on echocardiogram or MRI
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.

Source: Clinical Study 311 Protocol, Version 5, Amendment 4, Table 5 (b) (4)

Abbreviations: AV=atrioventricular; CDC=Centers for Disease Control and Prevention; cMRI=cardiac magnetic resonance imaging; ECG=electrocardiogram; ESC=European Society of Cardiology; MRI=magnetic resonance imaging.

1 Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed). 2 To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities

2. Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects.

3 Using either the original or the revised Lake Louise criteria (Ferreira 2018).

4 Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

5 Based on the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases (Adler 2015). https://academic.oup.com/eurheartj/article/36/42/2921/2293375

6 Typically descr bed as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur. Adapted from Gargano 2021.

Table 35. Potential Immune-Mediated Medical Conditions

Category	Diagnoses (as MedDRA Preferred Terms)
Neuroinflammatory Disorders	Acute disseminated encephalomyelitis (including site-specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), cranial nerve disorders including paralyses/paresis (eg, 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.

Category	Diagnoses (as MedDRA Preferred Terms)
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 thyroiditisa, diabetes mellitus type 1, Addison's disease.
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anemia, sarcoidosis.

Source: Protocol 2019nCoV-301 Version 8.0, Pages 172-173
Abbreviations: ANCA=anti-neutrophil cytoplasmic antibody; IgA=immunoglobulin A; MedDRA=Medical Dictionary for Regulatory Activities

Table 36. Adverse Events Representing Complications Specific to COVID-19[1]

Category	Diagnoses (as MedDRA System Organ Class/Preferred Term)
Respiratory/Infectious Disorders	ARDS, pneumonitis, septic shock-like syndrome.
Cardiac Disorders	Acute cardiac injury, arrhythmia.
Coagulopathy	Deep vein thrombosis, myocardial infarction, stroke.
Renal Disorders	Acute kidney injury.
Hematologic Disorder	Thrombocytopenia, septic shock-like syndrome.
Inflammatory Disorders	Cytokine Release Syndrome related to COVID-19 infection[2], multisystem inflammatory syndrome in children (MIS-C).
Neurologic Disorders	Generalized convulsions.

Source: Protocol 2019nCoV-301 Version 8.0, Pages 172-173.Abbreviations: ARDS=acute respiratory distress syndrome; COVID-19=coronavirus disease 2019; DAIDS=Division of AIDS; MedDRA=Medical Dictionary for Regulatory Activities.
1. COVID-19 manifestations associated with more severe presentation and decompensation with consideration of enhanced disease potential. The current listing is based on Coalition for Epidemic Preparedness Innovations /Brighton Collaboration Consensus Meeting (12/13 March 2020) and expected to evolve as evidence accumulates [Lambert 2020].
2. Cytokine release syndrome related to COVID-19 infection is a disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath [DAIDS, 2017].

The following pre-specified AESIs are under qualitative and quantitative surveillance by Novavax, per their Summary Safety Report, Version No.20, Review Period: August 1, 2023 to August 31, 2023, including observed-to-expected (O/E) analyses for signal generation.

- Acute disseminated encephalomyelitis
- Anaphylaxis
- Autoimmune hepatitis
- Autoimmune thyroiditis
- Bell's palsy
- Cerebral venous sinus thrombosis (CVST)
- Chronic fatigue syndrome
- Encephalitis, encephalomyelitis
- Fibromyalgia
- Fetal growth restriction
- Generalized convulsions
- Gestational diabetes

- Guillain-Barré syndrome (GBS)
- Hemorrhagic stroke
- Ischemic stroke
- Kawasaki's disease
- Major congenital anomalies
- Maternal death
- Microcephaly
- Multiple sclerosis
- Multisystem inflammatory syndrome in children
- Myasthenia gravis
- Myocardial infarction
- Myocarditis
- Myocarditis and pericarditis
- Pericarditis
- Narcolepsy
- Neonatal death
- Optic neuritis
- Postural orthostatic tachycardia syndrome (POTS)
- Preeclampsia
- Preterm birth
- Rheumatoid arthritis
- Spontaneous abortion
- Stillbirth
- Sudden death
- Thrombocytopenia
- Thrombosis with thrombocytopenia syndrome
- Transverse myelitis
- Vaccine-associated enhanced disease
- Venous thromboembolism

Other pre-specified safety topics under routine surveillance include:

- Death, all cause
- Cholecystitis
- Diarrhea
- Inflammatory eye disorders
- Herpes Zoster
- Menstrual disorders
- Paraesthesia
- Reactogenicity profile – second dose and boosters (based on impurity levels)
- Review of safety concerns in elderly and off-label pediatric use
- Vaccine anxiety-related reactions

11.2 Appendix B. Case Definitions

Table 37. COVID-19 Case Definitions

Severity	Case Definition
Mild	Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) New onset cough OR ≥2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalized muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhea
Moderate	High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days) Any evidence of significant LRTI: • Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) • Tachypnea: 24 to 29 breaths per minute at rest • SpO_2: 94% to 95% on room air • Abnormal chest X-ray or chest computerized tomography consistent with pneumonia or LRTI • Adventitious sounds on lung auscultation crackles/rales, wheeze, rhonchi, pleural rub, stridor)
Severe	Tachypnea: ≥30 breaths per minute at rest Resting heart rate ≥125 beats per minute Oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mm Hg High flow oxygen therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure) Mechanical ventilation or extracorporeal membrane oxygenation One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: • 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, pulmonary embolism • Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. • Admission to an intensive care unit • Death

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