Summary Basis for Regulatory Action

Date:	April 1, 2025
From:	CAPT Edward Wolfgang, PhD Review Committee Chair, OVRR/DRMMR
BLA STN:	STN 125817/0
Applicant:	Novavax Inc.
Submission Receipt Date:	April 1, 2024
PDUFA Action Due Date:	April 1, 2025
Proper Name:	COVID-19 Vaccine, Adjuvanted
Proprietary Name:	NUVAXOVID
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant, Office/Division
Chemistry, Manufacturing and Controls (CMC)	
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1. Introduction

This original BLA (STN 125817/0) was submitted by Novavax Inc. on March 29, 2024, to seek traditional approval of their COVID-19 Vaccine, Adjuvanted (NUVAXOVID) for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

A proprietary name request was included in the submission and the proposed proprietary name NUVAXOVID® was found acceptable. NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is to be administered intramuscularly as a single dose (0.5 mL).

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is a colorless to slightly yellow, clear to mildly opalescent sterile injectable suspension for intramuscular use that is free from visible particles. Each 0.5 mL dose of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024 – 2025 Formula) contains 5 mcg of recombinant spike (rS) protein of the SARS-CoV-2 Omicron variant lineage JN.1 and 50 mcg Matrix-M adjuvant. The Matrix-M adjuvant is composed of Fraction-A (42.5 mcg) and Fraction-C (7.5 mcg) of saponin extracts from the soapbark tree, *Quillaja saponaria* Molina. The rS protein is produced by recombinant DNA technology using a baculovirus expression system in the Sf9 insect cell line that is derived from the *Spodoptera frugiperda* species.

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is supplied in a pre-filled syringe (PFS) containing a singledose of 0.5 mL. Ten PFSs are supplied in a carton. The vaccine is stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and is not to be frozen.

The dating period for NUVAXOVID (2024 – 2025 Formula) supplied in PFSs is 3 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture of NUVAXOVID (2024 – 2025 Formula) shall be defined as the date when filling of the formulated drug product into syringes is initiated. The dating period for the rS drug substance for NUVAXOVID (2024 – 2025 Formula) shall be (b) (4) months when stored at (b) (4)

2. Background

COVID-19 is a disease caused by the SARS-CoV-2 virus [1]. A person with SARS-CoV-2 infection can present with respiratory symptoms that range in severity from mild to severe with some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome, leading to multiorgan failure and death, while others may be asymptomatic.

COVID-19 first emerged in Wuhan, China in late 2019 and rapidly resulted in a global pandemic [2]. SARS-CoV-2, the causative agent of COVID-19, infects a broad range of hosts and presents in humans with variable respiratory and systemic manifestations. SARS-CoV-2 continues to present a challenge to global health. As of March 16, 2025, SARS-CoV-2 had infected close to 778 million people worldwide resulting in more than 7.1 million COVID-19-related deaths [3]. As of June 1, 2024, nearly 1.2 million people in the U.S. had died of COVID-19 [1].

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is a nanoparticle vaccine that contains prefusion stabilized full-length recombinant spike (S) protein of the SARS-CoV-2. It also contains Matrix-M adjuvant comprised of saponins derived from the soapbark tree (*Quillaja saponaria Molina*). Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), which contained the recombinant spike (rS) protein from the Original (Wuhan Hu-1) SARS-CoV-2 strain, was authorized for use under Emergency Use Authorization (EUA) on July 13, 2022, for the prevention of COVID-19 in individuals 18 years of age and older (2-dose series in unvaccinated individuals). As SARS-CoV-2 evolved, the Novavax COVID-19 Vaccine, Adjuvanted (Formula) has been updated. On August 30, 2024, Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) was authorized for use under EUA in individuals 12 years of age and older with a dosing schedule based on vaccination status, including additional doses for individuals with certain kinds of immunocompromise. For further details, please refer to the Memorandum Supporting the Authorization.

Table 1. Regulatory History

Regulatory Event / Milestone	Date
Pre-IND meeting	April 14, 2020
IND submission	June 11, 2020
Fast Track designation granted	November 2, 2020
Pre-BLA meeting	April 14, 2023
BLA 125809/0 Submission	July 6, 2023
BLA 125809/0 Withdrawn by Applicant	August 22, 2023
BLA 125817/0 submission	April 1, 2024
BLA 125817/0 filed	May 30, 2024
Mid-Cycle communication	September 30, 2024
Late-Cycle meeting	December 17, 2024
Action Due Date	April 1, 2025

3. Chemistry, Manufacturing and Controls (CMC)

a. Product Quality

Description of NUVAXOVID (COVID-19 Vaccine, Adjuvanted)Active Ingredient
NUVAXOVID (COVID-19 Vaccine, Adjuvanted) contains a recombinant full-length SARS-CoV-2 spike glycoprotein (rS) that is stabilized in its prefusion conformation, as the active ingredient. The Original monovalent (NVX-CoV2373) contained the rS protein from the prototype (Wuhan-Hu-1 isolate of SARS-CoV-2); the 2023-2024 Formula (NVX-CoV2601) contained the rS protein from SARS-CoV-2 Omicron variant lineage XBB.1.5; and the 2024-2025 Formula (NVX-CoV2705) contains the rS protein from SARS-CoV-2 Omicron variant lineage JN.1. The rS antigen is expressed as a recombinant baculovirus (BACV) protein in *Spodoptera frugiperda* (Sf9) insect cells, purified by (b) (4) and (b) (4) chromatography and formulated into the rS drug substance (DS) in a formulation buffer containing disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, and polysorbate 80 (PS-80). The drug product (DP) contains rS DS co-formulated with Matrix-M (Matrix-M1) as an adjuvant. Matrix-M is prepared from saponin fractions (Fraction-A and Fraction-C) extracted from the bark of the soapbark tree, *Quillaja saponaria* Molina. The saponin

fractions (Fraction-A and Fraction C) are formulated into Matrix-A and Matrix-C drug substances by mixing with phosphatidylcholine and cholesterol to form cage-like structures (Matrix particles).

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) Manufacturing Overview

Clinical trial materials (CTMs, (b) (4) DP) for Phase 1/2 clinical development of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) were manufactured at small scale at Emergent BioSolutions Inc. (EBSI; Baltimore, Maryland). During Phase 3, rS DS CTMs were produced at (b) (4) scale at FujiFilm Diosynth Biotechnologies (FDBU; Research Triangle Park, North Carolina), while the DP was manufactured at PAR Sterile Products (PAR; Rochester, Michigan). The (b) (4) DS process and the DP process were transferred to the Serum Institute of India (SIIPL) for vaccine supply under Emergency Use Authorization, and for commercial production of NUVAXOVID (COVID-19 Vaccine, Adjuvanted). Subsequently, the DS process was scaled up to (b) (4)

Drug Substance for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) Manufacture of Recombinant SARS-CoV-2 S (rS) Protein

(b) (4)

(b) (4)

(b) (4)

Specifications for rS DS Release

The parameters evaluated for rS DS release, and their acceptance criteria are presented in Table 2.

Table 2. Specifications for the Release of rS DS for NUVAXOVID (COVID-19 Vaccine, Adjuvanted)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Matrix-M Adjuvant
Matrix-M is manufactured by mixing Matrix-A and Matrix-C adjuvant components, each produced from saponin materials: lyophilized Fraction-A and Fraction-C, respectively. Cholesterol and phosphatidylcholine are present as excipients in the Matrix-A and Matrix-C solutions. During early clinical development through Phase 3, Matrix-A and Matrix-C were manufactured at a small-scale in a single facility. Two additional facilities producing Matrix-A and Matrix-C at large scale were authorized to support emergency vaccine supply under the EUA. For the licensure application, Matrix-A and Matrix-C are sourced from two of these facilities and in-process, release, and characterization data for a minimum of (b) (4) process performance qualification batches of Matrix-A and Matrix-C manufactured from the two facilities were provided. Comprehensive analytical comparability assessments have been performed and the data submitted support the comparability of Matrix-A and Matrix-C manufactured at both facilities.

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) Drug Product

Description
NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP is a sterile, preservative-free suspension-for-injection in a PFS, containing rS protein of SARS-CoV-2 as the active ingredient. CMC information regarding three rS protein drug products are included in this licensure application. These are: the Original monovalent (NVX-CoV2373) vaccine which contained the rS protein from the prototype Wuhan-Hu-1 isolate of SARS-CoV-2; the 2023-2024 Formula which contained the rS protein from the SARS-CoV-2 Omicron variant lineage XBB.1.5; and the 2024-2025 Formula (NVX-CoV2705), which contained the rS protein from SARS-CoV-2 Omicron variant lineage JN.1. The NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP is an aqueous-buffered suspension of rS DS co-formulated with Matrix-M adjuvant in a formulation buffer containing disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, PS-80 and Water for Injection. The Matrix-M adjuvant contains Fraction-A and Fraction-C of saponin extracts derived from the soapbark tree, *Quillaja saponaria* Molina. The two fractions are separately formulated with cholesterol and phosphatidylcholine into

Matrix complexes (Matrix-A and Matrix-C). Matrix-A and Matrix-C are (b) (4) . The Original monovalent (Wuhan) DP was originally filled as a 10-dose (10DV) multidose vial presentation and subsequently as a 5-dose vial (5DV) presentation. Similarly, the 2023-2024 Formula (XBB.1.5 vaccine) was filled as a 5DV presentation whereas the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula) is filled as a single-dose PFS presentation.

The composition of NUVAXOVID (COVID-19 Vaccine, Adjuvanted), including excipients, is the same, irrespective of the vaccine strain/variant and presentation, except for the change in rS type. In addition, the original formulation target for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is a total protein concentration of (b) (4) µg/mL for a nominal dose of 5 µg rS antigen and 50 µg of Matrix-M per 0.5 mL. However, the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula) was reformulated at a target of (b) (4) µg/mL as the stability data indicated that the (b) (4) µg/mL formulation would have a shorter shelf life than the Wuhan and XBB.1.5 drug products. The NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP is stored at 2° to 8°C and administered by intramuscular injection in a volume of 0.5 mL. A list of the components of NUVAXOVID (COVID-19 Vaccine, Adjuvanted), including the active ingredient, adjuvant, and their quantities (per dose) and the function of each excipient is presented in Table 3.

Table 3. Composition of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) Drug Product

Ingredient	Function	Quantity per 0.5-mL dose	Reference to Quality Standard
SARS-CoV-2 Omicron JN.1 rS protein[1]	Immunogen/active ingredient	5 µg[2]	In-house
Matrix-M Adjuvant (total saponin)[3] Also containing:	Adjuvant	50 µg	In-house
Cholesterol[4]	Formulation agent	30.5 µg	(b) (4)
Phosphatidylcholine[4]	Formulation agent	23 µg	
Potassium dihydrogen phosphate[4]	Buffer	3.85 µg	
Potassium chloride[4]	Tonicity agent	2.25 µg	
Disodium hydrogen phosphate dihydrate[4]	Formulation buffer agent	14.7 µg	
Sodium Chloride[4]	Formulation buffer agent	(b) (4) µg	
Disodium hydrogen phosphate heptahydrate[5]	Formulation buffer agent	2.465 mg[6]	
Sodium dihydrogen phosphate monohydrate[5]	Formulation buffer agent	0.445 mg[6]	
Sodium Chloride[5]	Formulation Buffer agent –isotonicity adjuster	8.766 mg[6]	
Polysorbate 80[5]	Formulation Buffer agent – stabilizer	0.050 mg[6]	

Ingredient	Function	Quantity per 0.5-mL dose	Reference to Quality Standard
Sodium hydroxide	pH adjustment	q.s.	IP/ BP/ Ph. Eur.
Hydrochloric acid	pH adjustment	q.s.	IP/ BP/ Ph. Eur.
Water for Injection	Vehicle	q.s.	IP/ BP/ Ph. Eur./USP

[1]SARS-CoV-2 rS of prototype Wuhan strain in the Original monovalent, Omicron XBB.1.5 variant rS in the 2023-2024 Formula, and Omicron JN.1 variant rS in the 2024-2025 Formula.
[2]Nominal concentration.
[3]Matrix-M (Matrix-M1) = Matrix-A and Matrix-C components, in (b) (4) (by weight) proportion.
[4]Excipients used for Matrix; Phosphatidylcholine is derived from (b) (4) and contains (b) (4) α-Tocopherol antioxidant (DL-α-tocopherol) (per manufacturer's specification). A dose of NUVAXOVID containing 50 µg Matrix-M may contain a maximum of 50 ng α-Tocopherol.
[5]Excipients used for the DP formulation buffer. There are no (b) (4) for disodium hydrogen phosphate heptahydrate. Disodium hydrogen phosphate heptahydrate is listed as Sodium phosphate dibasic heptahydrate in supplier's CoA. Sodium dihydrogen phosphate monohydrate is listed as sodium phosphate monohydrate monobasic in supplier's CoA.
[6]Concentration of excipients to make the DP formulation buffer. Actual amount of these excipients in the final DP may vary by (b) (4) as Matrix-M adjuvant components are formulated in PBS.
q.s. = quantity sufficient; (b) (4)

Manufacture of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP

NUVAXOVID (COVID-19 Vaccine, Adjuvanted) was manufactured at PAR Sterile Products (PAR) during Phase 3 clinical development. Vaccine for emergency use under the EUA, and for commercial supply is manufactured at SIIPL. The formulation of the (b) (4) DP is the same for all variant vaccines except the rS protein, as well as the change in the formulation target for the JN.1 vaccine to (b) (4) µg/mL. The fill/finish operations for the Wuhan and XBB.1.5 DP in 5-dose multidose vials were identical. For the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula) DP, the fill/finish operations are different because of the use of a PFS container-closure system and filling in unit-dose.

Manufacturing Process Development

Like the rS DS, DP manufacture for Phase 1/2 clinical studies was performed at EBSI (at (b) (4) In the early Phase 1/2 product development, the rS antigen DP and the Matrix-M adjuvant were manufactured (b) (4) The Phase 3 DP was manufactured at PAR Sterile Products (Rochester Michigan) and transferred to SIIPL for vaccine supply under the EUA and for commercial vaccine manufacture. For the PAR and SIIPL DP processes, the rS DS is co-formulated with Matrix-M and filled into the final container as a co-formulated DP. The DP manufacturing process at PAR and SIIPL are similar. The process steps for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP manufacture are (b) (4) quality control testing and release, labelling/packaging and storage of the DP final container, and transportation of the DP. There is a (b) (4) operation step for the multidose vials and prefilled syringes due to the different container closure systems requiring the use of different equipment and a different fill-volume. The 10DV and 5DV presentations were filled in 5-mL (b) (4) type (b) (4) siliconized glass vials (with an average (b) (4) of (b) (4)) at a target of (b) (4) per vial and (b) (4), respectively. Vials are stoppered with uncoated, siliconized 13-mm bromobutyl rubber stoppers and crimped with 13-mm flip-off aluminum seal with blue plastic flip-off caps.

Each syringe of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) PFS presentation is filled at a target of (b) (4) mL in sterile, ready-to-fill 1-mL, round flange, siliconized

Type (b) (4) borosilicate glass syringe barrel with Luer-lock and plastic rigid tip cap with (b) (4) elastomer. The syringe plunger stopper is a (b) (4) and the plunger rod is made of polystyrene.

Formulation of the (b) (4) DP was performed at (b) (4) scale for the Wuhan 10DV and at (b) (4) scale for the 5DV of the Wuhan and XBB.1.5 drug products. The (b) (4) DP for the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula) PFS is formulated at (b) (4) scale. Validation of the DP manufacturing process was performed with the manufacture of (b) (4) process-performance qualification (PPQ) lots at each batch size (i.e., (b) (4) for the 10DV, (b) (4) for the 5DV, and (b) (4) for the PFS) at commercial scale. The (b) (4) and (b) (4) scales were originally validated with the Wuhan vaccine and the (b) (4) scale was verified for the XBB.1.5 vaccine. The PFS process was originally validated with XBB.1.5 vaccine manufactured in PFS presentation and subsequently validated for the (b) (4) µg/mL and (b) (4) µg/mL formulations of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula). All PPQ batches (a minimum of (b) (4) of each vaccine at the different manufacturing scales were within acceptance criteria or operational ranges for the various CPPs and IPCs evaluated at the various process steps of DP manufacture. The final containers from the DP process validation studies met all acceptance criteria for all quality attributes for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP release.

DP Comparability Assessment

A series of analytical comparability studies of DP lots manufactured for process-validation were performed. The Original monovalent 10DV batches manufactured at SIIPL were compared with Original monovalent 10DV DP batches manufactured at PAR; the 5DV Original monovalent lots were compared with the 10DV Original monovalent lots manufactured at SIIPL; and the 5DV 2023-2024 Formula (XBB.1.5 vaccine) was compared with the 5DV Original monovalent. Analytical comparability of the 5DV and PFS presentations of the XBB.1.5 DP was performed to assess the impact of manufacturing operational changes (primarily at the filling step) on the quality attributes of the DP. Analytical comparability of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula) in PFS presentation with the XBB.1.5 vaccine 5DV (which has been used in clinical trials) was performed. In all comparability assessments, the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP batches from different facilities and/or in different presentations as described above met their respective acceptance criteria for the various quality attributes for vaccine release.

Stability of the Nuvaxovid (COVID-19 Vaccine, Adjuvanted) DP

Available real-time stability data supported the 9-month shelf-life request for the Original monovalent (Wuhan) and the 2023-2024 Formula (XBB.1.5) under long-term storage condition at 2° to 8 °C. The 2024-2025 Formula (JN.1) in PFS presentation is relatively less stable and was authorized for a 3-month shelf life under the EUA. All commercial lots of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP manufactured at (b) (4) µg/mL are placed under stability monitoring for a minimum of 1 month and must meet a statistically calculated relative potency of (b) (4) at the 1-month timepoint to be released. A total of (b) (4) lots (b) (4) PPQ and (b) (4) commercial lots) of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP in PFS are under long-term stability evaluation. Real-time stability data through the (b) (4) month timepoint for (b) (4) lots (b) (4) PPQ and (b) (4) commercial lots) show an average relative potency of (b) (4), with (b) (4) of (b) (4) lots having a relative potency of (b) (4) (i.e., below the stability lower limit of (b) (4)). The available real-time stability data support the 3-

month shelf-life request for the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) (2024-2025 Formula).

b. Testing Specifications

The analytical test methods used for the release and stability evaluation of the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP are summarized in Table 4.

Table 4. Specifications for the Release and Stability Evaluation of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DP

Quality Attribute	Test Method	Acceptance Criteria for DP Release	Acceptance Criteria for DP Stability
Appearance	Visual observation (b) (4)	Color: Colorless (b) (4) Clarity: Clear (b) (4) Free from visible particles	Color: Colorless (b) (4) Clarity: Clear (b) (4) Free from visible particles
pH	(b) (4)		
(b) (4)			
Particle size[1, 1a]	(b) (4)		
Expelled volume[2]	(b) (4)	The volume measured for each container is not less than the nominal volume.	N.A.
Identity[3]	(b) (4)	Identity confirmed	Identity confirmed
	(b) (4)	Identity confirmed	Identity confirmed
Total Protein[4] Concentration	(b) (4)	(b) (4)	
Relative Potency[5]	(b) (4)	(b) (4) potency, relative to reference standard[2]	(b) (4) potency, relative to reference standard
Matrix-A Content	(b) (4)		
Matrix-C Content	(b) (4)		
Endotoxin	(b) (4)		N.A.
Sterility	(b) (4)	No growth	No growth
Container-Closure Integrity	Container Closure Integrity Test (CCIT) (b) (4)	N.A.	No failure allowed

Quality Attribute	Test Method	Acceptance Criteria for DP Release	Acceptance Criteria for DP Stability
(b) (4)		N.A.	(b) (4)

[1]Applicable to the release of the PFS presentation.
[1a]Particle size testing was used for the release of the XBB.1.5 DP and it is used in stability evaluation of Wuhan and variant DPs.
[2]The multidose 10DV and 5DV presentations are tested for "*Extractable Volume*" under the same compendial reference, with the acceptance criterion as "*The volume should be such that each syringe delivers not less than stated doses*".
[3]Only one identity testing method is used at a time. (b) (4) is used during early product development. (b) (4) is used when specific antibody reagents become available.
[4]For emergency vaccine supply under the EUA, the Original monovalent (Wuhan) DP was tested for release by (b) (4) assay. Due to assay variability and shortage of the (b) (4) assay reagent, an (b) (4) was used for the release of the 2023-2024 Formula (XBB.1.5 vaccine DP). Subsequently, the (b) (4) assay was developed. In bridging studies performed using XBB.1.5 DP lots, the 3 assays (b) (4) were demonstrated to be statistically equivalent. The release and stability specification for both (b) (4) are the same. A specification range of (b) (4) was used for the release and stability evaluation of the XBB.1.5 vaccine by the (b) (4) method.
[5]For variant (XBB.1.5 and JN.1) DP release, relative potency testing is performed (b) (4) -manufacture to allow for (b) (4) . A specification of (b) (4) was originally requested for the JN.1 vaccine but was further revised to (b) (4) based on statistical analysis, with the lower release specification allowing for the JN.1 DP to be at or above the lower limit of (b) (4) relative potency in the stability program at the end of shelf life. The Original monovalent was released with a specification of (b) (4) for the EUA. The specification was revised to (b) (4) based on statistical analysis as more stability data became available. A specification of (b) (4) was used for the release of the XBB.1.5 under the EUA when the XBB.1.5 vaccine was tested for relative potency against Wuhan interim reference standard (lot (b) (4)). The release specification was revised to (b) (4) after a qualified XBB.1.5 reference standard became available.
(b) (4)
N.A. = Not Applicable; CCIT = Container Closure Integrity Test; (b) (4) ; mL = Milliliters; ug = Micrograms; (b) (4) .

The analytical methods and their validations and/or qualifications reviewed for the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is listed with the activities performed and inspectional histories noted in the table below.

Table 5. Manufacturing Facilities for NUVAXOVID (COVID-19 Vaccine, Adjuvanted)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
Serum Institute of India Pvt. Ltd. (b) (4) Drug Substance (DS) and Drug Product (DP) manufacturing, packaging, Quality Control (QC) batch release and stability testing. DP visual inspection and labeling.	(b) (4)		PLI	CBER DMPQ (b) (4) VAI
(b) (4) DP: QC Batch Release and Stability testing (Identity by (b) (4))	(b) (4)		Waiver	(b) (4) GMP Inspection (b) (4) GMP Certificate issued
(b) (4) DP: QC Batch Release Testing (expelled volume) for Prefilled Syringe	(b) (4)		Waiver	ORA (b) (4) NAI

CBER conducted a facility inspection of the SIIPL facility in (b) (4), and a Form FDA 483 was issued at the conclusion of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as VAI.

In (b) (4), inspected the contract testing laboratory, (b) (4) for conducting chemical/physical, biological and microbiological Quality Control testing, and issued Certificate of GMP Compliance of Manufacture Certificate (Certificate No. (b) (4)

ORA conducted a surveillance inspection of the contract testing laboratory, (b) (4), and no Form FDA 483 was issued at the conclusion of the inspection. The inspection was classified as NAI.

e. Container/Closure System

Table 6. Container Closure Systems for the NUVAXOVID (COVID-19 Vaccine, Adjuvanted) Drug Product

Component	Manufacture	Description	Standards
Glass vial	(b) (4)	5 mL clear, (b) (4) type (b) (4) glass siliconized vials	(b) (4)
Rubber stopper	(b) (4)	13 mm bromobutyl uncoated, siliconized, ready for sterilization rubber stoppers	(b) (4)

Component	Manufacture	Description	Standards
Aluminum seal	(b) (4)	13 mm flip off aluminum seal with blue colored plastic cap	Non- product contact
Glass Syringe	(b) (4)	1 mL Standard, Round Flange, Siliconized Type (b) (4) borosilicate glass syringe barrel with Luer lock and Plastic Rigid Tip Cap with (b) (4) Elastomer, sterile, ready to use	(b) (4)
Plunger Stopper	(b) (4)	(b) (4)	(b) (4)
Plunger Rod	(b) (4)	Polystyrene plunger rod	Non-product contact

The glass vials are washed, dried and depyrogenated onsite prior to use and the rubber stoppers are autoclaved onsite prior to use. The container closure integrity of the filled vials was tested on-site by (b) (4) method during shelf-life study on final products. The acceptance criteria for container closure integrity were met. In a communication dated October 18, 2025, Novavax confirmed that the JN.1 (2024-2025 Formula) will only be available as a PFS presentation and not as a multi-dose vial (MDV) presentation.

The PFS, stoppers and plungers are supplied Ready-to-Use (RTU). The container closure integrity of the filled PFS was tested by a contract testing laboratory, (b) (4) using a (b) (4) method during shelf-life study. The acceptance criteria of container closure integrity were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology Studies

The Wuhan and variant rS DS batches were tested for immunogenicity in several nonclinical studies in mice, hamsters, and non-human primates (NHPs). The effect of Matrix-M adjuvant on the immune response induced by rS was evaluated in nonclinical studies. In a study in mice, animals were vaccinated with Wuhan rS with or without Matrix-M adjuvant on a prime and boost schedule at an interval of 21 days. One group was vaccinated with 10 µg of BV2373 (Wuhan rS) without Matrix-M. A second group was vaccinated with 10 µg of BV2373 adjuvanted with 5 µg of Matrix-M. A third group was injected with placebo (formulation buffer). Serum samples obtained a day before the first dose and on study days 20 and 28 were tested for rS-specific IgG and ACE2 binding-inhibiting antibodies. rS-specific IgG antibody and ACE2-binding inhibiting antibody were not detected at any timepoint in the placebo group. rS-specific IgG antibody was >50-fold higher in the adjuvanted rS group than the unadjuvanted rS group on Day 20, and >70-

fold higher on Day 28. Similarly, the adjuvanted rS group had >30-fold higher level of ACE-binding inhibiting antibody than the unadjuvanted rS group at both Day 20 and Day 28. In another study, mice vaccinated with adjuvanted Wuhan rS (0.01 µg, 0.1 µg, 1.0 µg, and 10 µg) had higher antibody levels, including SARS-CoV-2 neutralizing antibody, than those vaccinated with 10 µg of unadjuvanted rS, and were better protected from weight loss and lung virus load than mice vaccinated with 10 µg of unadjuvanted Wuhan rS, following a subsequent infection with SARS-CoV-2. Similar results were obtained in (b) (4) baboons, where animals vaccinated with adjuvanted Wuhan rS induced significantly higher antibody levels than animals vaccinated with unadjuvanted rS. This set of studies indicate that the Matrix-M adjuvant is critical in enhancing the immune response induced by rS.

Effectiveness of the Wuhan rS DS in protecting animals from disease upon challenge with SARS-CoV-2 postvaccination was investigated in (b) (4) hamsters and NHPs. Data from these studies indicate that Wuhan and variant rS adjuvanted with Matrix-M induce high antibody responses in animals, including rS-specific IgG, ACE2-binding inhibiting antibodies, and neutralizing antibodies, as well as cell mediated immune responses, with a dominant Th1-type $CD4^+$ T-cell responses, including polyfunctional effector T cells. While the total IgG response against each strain cross-reacts with the rS of other strains and/or variants or sub-lineages, IgG titers are typically at higher levels against the homologous rS. However, neutralizing antibodies are mostly strain- or variant-specific. In hamsters and non-human primates, the adjuvanted Wuhan rS protected animals from weight loss, and facilitated a rapid clearance of SARS-CoV-2 in immunized animals compared with unimmunized (placebo-treated) animals. In animals vaccinated with low doses (i.e., 0.01 µg, 0.1 µg or 1 µg) of Wuhan rS prior to challenge with SARS-CoV-2, no evidence of exacerbation of disease was found in necropsy and histopathology, thus alleviating earlier concerns about potential occurrence of vaccine-induced enhanced disease in vaccine recipients after a subsequent exposure to SARS-CoV-2.

Assessment of Intramuscular Toxicity Study

In the 57-day repeat intramuscular toxicity study, rabbits were administered intramuscularly 4 doses (3 weekly and one additional 21 days later) of 50 ug SARS-CoV-2 rS with 50 ug Matrix-M or 50 ug Matrix-M alone. Vaccine was well tolerated by animals. There were no biologically significant effects of the adjuvanted vaccine on clinical observations, mortality, body weights, food consumption, body temperature, ophthalmology, coagulation, organ weights and macroscopic examination. Transient elevations of C-reactive protein (CRP) and fibrinogen and local inflammation reactions were observed at the injection sites, indicative of acute reactions as expected.

Developmental Assessment and Reproductive Toxicology (DART) Study

In the developmental toxicity study of SARS-CoV-2 rS, female rats were administered intramuscularly 5 ug SARS-CoV-2 rS with 10 ug Matrix-M1 or 10 ug Matrix-M1 alone in 0.1 mL at 27 days and 13 days prior to mating and on gestation Days 7 and 15. There were no effects on mating performance, fertility, fetal weight, or natural delivery. No increased effects were observed in fetal external, visceral or skeletal malformations or changes in postnatal development.

Other Supportive Toxicology Studies
Two genotoxicity studies were conducted with Matrix-M1 adjuvant at (b) (4) mg/mL and (b) (4) mg/mL concentrations. At concentrations up to (b) (4) mg/mL ((b) (4) µg per (b) (4)), it was negative in the (b) (4) test for all test strains except strain (b) (4) in the absence of (b) (4) for which testing was limited to up to (b) (4) mg/mL due to contamination. It was also negative at concentration up to (b) (4) mg/mL ((b) (4) ug/mL per (b) (4)) for induction of (b) (4) test using (b) (4).

There were no safety concerns or potential risks identified based on nonclinical safety data. Overall, the nonclinical safety assessment for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) was considered acceptable to support licensing from a toxicological standpoint.

5. Clinical/Statistical

Clinical Diagnostic Assays Used to Support Primary Clinical Efficacy Endpoints
During the clinical development of NUVAXOVID (COVID-19 Vaccine, Adjuvanted), clinical diagnostic assays were used to evaluate vaccine effectiveness. The *SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction* which uses the Abbott RealTime SARS-CoV-2 RT-PCR kit for the quantitative detection of SARS-CoV-2 infection in clinical samples by targeting the amplification of the SARS-CoV-2 nucleocapsid (N) gene was used to detect SARS-CoV-2 (Wuhan strain) infection. The assay was validated at the (b) (4)) where diagnostic support for clinical trials was provided.

The *Roche Elecsys Anti-SARS-CoV-2 N antibody assay* was used for the qualitative detection of antibodies against the N protein of SARS-CoV-2 in clinical serum and plasma samples and was used in determining the SARS-CoV-2 serostatus of study subjects. Both testing kits were authorized for emergency use and were validated at the (b) (4). A whole genome sequencing of clinical isolates of SARS-CoV-2 for the purpose of detecting virus variants was performed on an ad-hoc basis at the (b) (4) to support the diagnosis of SARS-CoV-2.

Immunogenicity Assays
The evaluation of immune response in the clinical studies is based primarily on the assessment of neutralizing antibody induced by the rS antigen. During Phase 3, a validated *in vitro* microneutralization assay based on the neutralization of a clinical isolate of the Wuhan strain was used. Subsequently, pseudovirus neutralization assays have been developed and validated to support clinical trials of the XBB.1.5 and JN.1 vaccines. In addition, a spike protein-specific IgG ELISA for measuring the total IgG antibody response and an ACE2-binding inhibition ELISA for measuring levels of antibodies capable of blocking the binding of rS to the human ACE2 receptor were developed and validated. Cell-mediated ($CD4^+$ and $CD8^+$ T-cell) immune responses were assessed by interferon-gamma ELISpot and intracellular cytokine staining.

a. Clinical Program

Overview of Clinical Studies
Studies submitted in the BLA are summarized in Table 7. Study 2019nCoV-301 serves as the primary evidence of safety and effectiveness of the primary series regimen and

the booster regimen of NVX-CoV2373 (Original Wuhan formulation) in adults and adolescents. Study 2019nCoV-311 provides evidence of safety and immunogenicity of the SARS-CoV-2 subvariant based formulation, and study 2019nCoV-313 provides evidence of the safety and immunogenicity of the single dose indication. The rest of the studies are included in the ISS as supportive evidence of safety of NVX-CoV2373.

Table 7. Clinical Studies Supporting the BLA

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

Study Number (Status) Countries	Phase/Study Design	Test Product (Dose)	Number of Subjects (Randomized)	Study Population
2019nCoV-311 Part 2 (ongoing) Australia Initiated: March 22, 2023 Data Cutoff Date: May 31, 2023	Phase 3 randomized, observer-blind study evaluating the safety and immunogenicity of 2 booster doses (Day 0 and Day 90) of NVX-CoV2540 (Omicron BA.5) and NVX-CoV2373 Original Wuhan) alone and bivalent NVX-CoV2373 + NVX-CoV2540 (Original Wuhan/BA.5) vaccine in previously vaccinated adults ≥ 18 years of age.	NVX-CoV2540 (5 µg, Omicron BA.5) NVX-CoV2373 (5 µg, Original Wuhan) NVX-CoV2373 + NVX-CoV2540 (5 µg, Original Wuhan/BA.5) Bivalent Vaccine	NVX-CoV2540: N=255; NVX-CoV2373: N=252; NVX-CoV2373 + NVX-CoV2540: N=259;	Adults ≥18 years of age who had received a regimen of ≥3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously.
2019nCoV-313 (Part 1) USA Initiated: September 7, 2023 Data Cutoff Date: October 16, 2023	Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant) in adult participants ≥ 18 years of age previously vaccinated with an mRNA COVID-19 vaccine.	1 booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant)	NVX-CoV2601: N=332	Adults ≥18 years of age, previously vaccinated with an mRNA COVID-19 vaccine
2019nCoV-313 (Part 2) (completed) USA Initiated: September 18, 2023 Completion Date: May 20, 2024	Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant) in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve adult participants ≥ 18 years of age.	1 dose of NVX-CoV2601 (Omicron XBB.1.5 subvariant)	NVX-CoV2601: N=338	Adults ≥ 18 years of age, baseline SARS-CoV-2 seropositive, COVID-19 vaccine naïve
2019nCoV-307 (completed) USA Initiated: July 11, 2022 Completion date: August 24, 2022	Phase 3, randomized, observer-blinded, lot-to-lot consistency immunogenicity and safety study in previously vaccinated, medically stable adults, 18 through 49 years of age.	3 different manufacturing lots of NVX-CoV2373 (5 µg, Original Wuhan)	NVX-CoV2373: N=911	Previously vaccinated, medically stable adults, 18 through 49 years of age.
2019nCoV-101 Part 1 (completed) Australia Initiated: May 6, 2020 Completion date: June 26, 2021	Phase 1, randomized, observer-blinded, placebo-controlled study of the safety and immunogenicity of NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation) with or without Matrix-M adjuvant (50 µg) in healthy adults (18 through 59 years of age), with no history of SARS-CoV-2 infection or COVID-19.	NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation)	NVX-CoV2373 (5 µg with Matrix-M adjuvant [50 µg] - (b) (4) scale formulation): N=29 Placebo: N=25	Healthy adults, 18 through 59 years of age, with no history of SARS-CoV-2 infection or COVID-19

Study Number (Status) Countries	Phase/Study Design	Test Product (Dose)	Number of Subjects (Randomized)	Study Population
2019nCoV-101 Part 2 (ongoing) USA, Australia Initiated: August 24, 2020 Data cutoff date: June 1, 2022	Phase 2, randomized, observer-blinded, placebo-controlled study of the safety and immunogenicity of 4 dose regimens of NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation) with Matrix-M adjuvant (50 µg) and of 6- and 12-month booster regimens in healthy adults (18 through 84 years of age), with no history of SARS-CoV-2 infection or COVID-19 resulting in medical intervention (mild COVID-19 was allowed)	NVX-CoV2373 (5 µg and 25 µg - (b) (4) scale formulation)	NVX-CoV2373: N=514 Placebo: N=255	Healthy adults (18 through 84 years of age), with no history of SARS-CoV-2 infection or COVID-19 resulting in medical intervention (mild COVID-19 was allowed)
2019nCoV-302 (completed) United Kingdom Initiated: September 28, 2020 Completion date: March 29, 2022	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of NVX-CoV2373 ((b) (4) scale formulation) in healthy and clinically stable adults (18 through 84 years of age) in the United Kingdom (UK).	NVX-CoV2373 ((b) (4) scale formulation)	NVX-CoV2373: N=7592 Placebo: N=7593	Healthy and clinically stable adults, 18 through 84 years of age in the UK
2019nCoV-501 (completed) South Africa Initiated: August 17, 2020 Completion date: August 13, 2021	Phase 2, randomized, observer-blinded, placebo-controlled efficacy, safety and immunogenicity study of NVX-CoV2373 ((b) (4) scale formulation) in healthy HIV-negative adults 18 through 84 years of age and medically stable people living with human immunodeficiency virus (PLWH) 18 through 64 years of age, with negative PCR test result within 5 days prior to first vaccination.	NVX-CoV2373 ((b) (4) scale formulation)	NVX-CoV2373: N=2213 Placebo: N=2206	Healthy HIV-negative adults 18 through 84 years of age and medically stable PLWH 18 to 64 years of age, with negative PCR test result within 5 days prior to first vaccination

Study 301

Study 301 was a Phase 3, saline placebo-controlled, randomized (2:1), observer-blind study of a 2-dose series of the Original Monovalent vaccine in previously unvaccinated adults and adolescents (pediatric expansion) conducted in the United States (U.S.) and Mexico. Efficacy was assessed using a clinical endpoint: polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination of the initial vaccination period.

Vaccine efficacy in adults, based on data from approximately 30,000 adults accrued through September 27, 2021, had a point estimate of 89.6%, 95%CI (82.5, 93.8). After study initiation, the protocol for Study 301 was revised to include a blinded crossover vaccination period, which was initiated on 20 April 2021. During the blinded crossover vaccination period, 15,319 (77.7%) participants who received Original Monovalent during

the initial vaccination period crossed over to receive placebo (Original Monovalent to placebo) and 6,395 (64.8%) participants who had received placebo crossed over to receive Original Monovalent (placebo to Original Monovalent), with nearly 99% of participants who crossed over receiving both doses of trial vaccine. In the pre- and post-crossover period, all unsolicited adverse events (AEs) and medically attended adverse events (MAAEs) were collected through 49 days post-Dose 1, and MAAEs attributed to study vaccine, serious AEs (SAEs), and AEs of special interest (AESIs, defined as COVID-related AEs and potential immune-mediated medical conditions [PIMMCs]) were collected for the duration of the study in all participants. The total safety database for NVX-CoV2373 from clinical trials includes approximately 45,000 participants who received at least one dose of vaccine. The safety analysis population in Study 301 included participants who received at least 1 dose of Original Monovalent in the pre-crossover period (N=29,582; 19,735 Original Monovalent, 9,847 placebo; median follow-up 2.5 months post-Dose 2 based on data extraction date of August 18, 2022) or post-crossover period (N=21,714; 6,416 Original Monovalent crossover, 15,298 placebo crossover; median follow-up 8.4 months post-Dose 4 based on data extraction date of February 17, 2022). Solicited adverse reactions (ARs), most common being injection site pain/tenderness, fatigue, headache, and muscle pain, were reported by a higher percentage of Original monovalent recipients than placebo recipients, were reported more frequently after Dose 2 than Dose 1 and were reported more frequently by younger adults (18 through 64 years of age) than older adults (≥65 year of age) who received Original monovalent. Severe local and systemic ARs were more frequent after Dose 2 (7.2% and 12.1%, respectively) than Dose 1 (1.2% and 2.4%, respectively). In the blinded, placebo-controlled pre-crossover period, the percentages of participants reporting unsolicited AEs, MAAEs, and SAEs were comparable between the NVX and placebo arms. There were 3 cases of myocarditis/ pericarditis reported within 14 days after Dose 2 of Original Monovalent compared with 1 case in the placebo arm. These events are included in postmarketing requirements for ongoing safety assessment.

Study 301 pediatric expansion evaluated both immunogenicity and clinical efficacy of a 2-dose series of the Original Monovalent vaccine compared with saline placebo in approximately 2200 adolescents 12 through 17 years of age. Neutralizing antibody responses at Day 14 post-Dose 2 against the ancestral (Wuhan) pseudovirus in the adolescents were compared with those from adults in Study 301, and the analyses met noninferiority criteria (i.e., pre-specified lower limits of the 95% CI for geometric mean titer ratios (GMTR) and percentage difference in seroresponse rates). Vaccine efficacy against PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination was estimated to be 79.8%, 95%CI (47.5, 92.2). The safety analysis population for Study 301 Pediatric Expansion included adolescents 12 through 17 years of age who received at least one dose of Original Monovalent in the pre-crossover period (N=2,232; 1487 Original Monovalent, 745 placebo) or post-crossover period (N=2,018; 665 Original Monovalent crossover, 1,353 placebo crossover). In the pre-crossover period, the median follow-up post-Dose 2 was 71 days and in the post-crossover period, the median follow-up post-Dose 4 was 30 days. Solicited ARs were reported by a higher percentage of Original Monovalent recipients than placebo recipients, and more frequently after Dose 2 than Dose 1. The most frequently reported severe local and systemic ARs were injection site pain/tenderness and fatigue/malaise, respectively. One serious event of myocarditis in Study 301 pediatric expansion was reported in an adolescent male 2 days after Dose 2. No deaths were reported during the study.

Study 311

Adults

Study 311 Parts 1 and 2 enrolled individuals who were previously vaccinated with either 2 or 3 doses of mRNA vaccines. These studies were analyzed to support the safety and effectiveness of updated monovalent BA.1 and BA.5 vaccines. Immunobridging analyses from Study 311 parts 1 and 2 supported the effectiveness of the updated BA.1 and BA.5 monovalent vaccines in previously vaccinated adults. The effectiveness of the updated monovalent BA.1 and BA.5 vaccines, given as a 2-dose series, was extrapolated to unvaccinated adults, based on the analyses from Study 311 Parts 1 and 2 and data from Study 301 [which demonstrated noninferiority of immune responses between individuals who received the 2-dose primary series and previously vaccinated individuals who received a third (booster dose)]. The safety data from Study 311 Parts 1 and 2 did not reveal any new safety findings in adults who received the updated BA.1 and BA.5 monovalent vaccines when compared with individuals who received the Original Monovalent vaccine. The safety of the updated BA.1 and BA.5 monovalent vaccines is also supported by the safety data for the Original Monovalent vaccine from the Adult portion of Study 301.

Pediatrics

The effectiveness of the updated monovalent BA.1 and BA.5 vaccines in adults, given as a 2-dose series in unvaccinated individuals and as a single dose in previously vaccinated individuals, was extrapolated to adolescents 12 through 17 years of age based on Study 311 part 1 and 2 immunobridging data, the descriptive efficacy data supporting the 2-dose Original Monovalent vaccine primary series in adolescents from the adolescent portion of Study 301, and immunogenicity analyses from the adolescent portion of study 301 (which included the non-inferiority analysis of immune responses between adults and adolescents supporting 2-dose Original Monovalent primary series in adolescents and the noninferiority analysis of immune responses between vaccine-naive adolescents who received the 2-dose Original Monovalent primary series and previously vaccinated adolescents who received the Original Monovalent vaccine as a third dose, supporting the “booster” dose in adolescents). The safety of the updated monovalent BA.1 and BA.5 vaccines in adolescents is supported by the safety data from Study 311 Parts 1 and 2 in adults and the safety data in adolescent portion of Study 301 for the Original Monovalent vaccine.

Switch in Dosing Regimen – Two Doses to a Single Dose in COVID-19 vaccine Naïve Seropositive Individuals:

In May 2023, CBER requested that the Applicant conduct a post hoc analysis of immunogenicity data post-Dose 1 from Study 301 to evaluate the effectiveness of a single dose of Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) in the unvaccinated, baseline seropositive population of 792 individuals. The analysis was conducted using a validated Monogram pseudovirus neutralization assay to assess post-dose immune responses. The post hoc, descriptive, noninferiority analysis of the immune responses, as measured by GMT ratios and percentage difference in SCR, induced by Original monovalent vaccine in baseline seropositive individuals 21 days post-Dose 1 compared with baseline seronegative adults 35 days post-Dose 2 against the ancestral (Wuhan-Hu-1) strain did not meet the > 0.67 lower bound of the 95% confidence

intervals that would have been necessary to demonstrate noninferiority based on the GMT ratio in participants 12 years and older [GMTR 0.61 (95% CIs: (0.54, 0.68)]. Noninferiority criteria, analyzed descriptively, also did not meet the > -10.0% expected lower bound of the 95% CIs that would have been necessary to demonstrate noninferiority based on the percentage difference in SCRs in participants 12 years and older [% difference in SCR -12.0% (95% CIs: -14.7, -9.3)]. Based on these results submitted in August 2023, CBER concluded that there was insufficient evidence to demonstrate that single dose of Novavax COVID-19 Vaccine, Adjuvanted in COVID-19 vaccine-naïve seropositive individuals restores effectiveness in protection against circulating SARS-CoV-2 variants and that a 2-dose regimen would be required in these individuals.

The Applicant adapted Study 313 to conduct a prespecified noninferiority analysis comparing the GMTs and SRRs of previously vaccinated individuals and baseline seropositive vaccine naïve individuals, which met noninferiority criteria for success (see description below and section 6.5 of the clinical memorandum for further details), thereby demonstrating the effectiveness of a single dose of Novavax COVID-19 Vaccine (Adjuvanted) in seropositive, COVID-19 vaccine-naïve individuals. The final study report for Study 313 Part 2 became available in October of 2024, post August 2024 authorization of the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) to be administered as a 2-dose regimen in COVID-19 vaccine-naïve individuals and 1-dose regimen in previously COVID-19 vaccinated individuals. When submitted to CBER on December 9, 2024 (IND 22430, SN 703), it was reviewed as part of this BLA.

The success of the noninferiority analysis in Study 313 part 2 may be explained by the exposure of the U.S population to multiple subvariants of SARS-CoV-2 virus [e.g., Alpha, Delta, Omicron, XBB.1.5], and were primed to generate more robust immune responses after single-dose vaccination at the time of Study 313 enrollment compared with the timing of Study 301 in 2020, when much of the U.S. population may have only been exposed to Wuhan-Hu-1 isolate of SARS-CoV-2.

Study 313

Adults

Immunogenicity data that support a single dose of the 2024-2025 Formula (JN.1) in individuals 18 years of age and older regardless of vaccine history comes from Study 313 Part 2, which enrolled COVID-19 vaccine-experienced individuals 18 years and older. Neutralizing antibody responses induced by a single-dose regimen of the 2023-2024 Formula (Omicron XBB.1.5) in baseline seropositive COVID-19 vaccine-naïve adults were compared with responses in previously mRNA COVID-19 vaccinated adults. Noninferiority success criteria were met for immune responses, indicating effectiveness of a single dose regardless of vaccination history. The safety data that support a single dose of the 2024-2025 Formula (JN.1) in individuals 18 years of age and older regardless of vaccine history comes from the overall safety data base, including adult portion of Study 301, Study 313 parts 1 and 2, and Study 313 parts 1 and 2.

Adolescents

The effectiveness of a single dose of the 2024-2025 Formula (JN.1) was extrapolated from adults aged 18 years and older to adolescents based on the immunogenicity data

from Study 313 part 2 in adults along with the immune bridges from Study 311 parts 1 and 2, and the descriptive efficacy and immunogenicity data from the adolescent portion of Study 301 as discussed above. The safety data from the adolescent portion of Study 301 for the Original Monovalent vaccine support the safety of the single dose of the 2024-2025 Formula (JN.1) in adolescents.

Across all studies submitted to this BLA, important risks that are identified with NUVAXOVID (COVID-19 Vaccine, Adjuvanted) include myocarditis and/or pericarditis (important identified risk), ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves IV and VI) and vestibular neuronitis (i.e., affecting cranial nerve VIII), atrial fibrillation and cerebrovascular accidents (CVA) (important potential risk). See *Post-Authorization Safety Surveillance* below for additional information.

Effectiveness of Novavax COVID-19 Vaccine, Adjuvanted, Bivalent Formulations

Study 311 was a Phase 3, randomized, observer-blinded study designed to assess the effectiveness of bivalent formulations of Novavax COVID-19 Vaccine, Adjuvanted. Neither the prespecified noninferiority analysis of the bivalent vaccine (Original and Omicron BA.1) compared with the monovalent vaccine (Omicron BA.1) vaccine nor the descriptive noninferiority analysis of the bivalent vaccine (Original and Omicron BA.5) compared with the monovalent vaccine (Omicron BA.5) succeeded in demonstrating noninferiority. Based on the available data, there is insufficient evidence to conclude that the bivalent vaccine technology would be effective for future formulations.

For details, please refer to Clinical Review Memorandum, Section 6.4.13.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspections were issued for two Clinical Investigator study sites that participated in the conduct of Study 2019nCoV-301. The inspections did not reveal significant issues that impact the data submitted in this BLA.

c. Pediatrics

To address requirements of the Pediatric Research Equity Act, the Applicant submitted a request for deferral of the following studies in pediatric individuals <12 years of age because NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is ready for approval for use in adults and the pediatric studies have not been completed. The deferred studies are:

Deferred pediatric study 2019nCoV-503 to evaluate the safety and immunogenicity of NUVAXOVID in COVID-19 vaccine-naïve individuals 6 months to <12 years of age.

Deferred pediatric study under PREA (Study 2019nCoV-317) to evaluate the immunogenicity of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) in COVID-19 vaccine-naïve seropositive individuals 2 years to <12 years of age and to evaluate the safety and immunogenicity of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) in individuals 6 months to <2 years of age, using a contemporaneously vaccinated comparator group.

Deferred pediatric study under PREA (Study 2019nCoV-506) to evaluate the safety and immunogenicity of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) in COVID-19 vaccine-naïve individuals 0 to <6 months of age.

6. Safety and Pharmacovigilance

Post-Authorization Safety Surveillance

VAERS was queried for AE reports following administration of the Novavax COVID-19 Vaccine, Adjuvanted, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was due to the vaccine.

As of October 18, 2024, a total of 1,017 reports to VAERS related to the Novavax COVID-19 Vaccine, Adjuvanted were received and processed (coded, redacted, and quality assurance performed). Among these, 54.8% (557 reports) were reports of SAEs. The most common SAEs reported to VAERS were headache (n=71, 7%), chest pain (n=61, 6%), dyspnoea (n=58, 5.7%), dizziness (n=57, 5.6%), fatigue (n=54, 5.3%), myalgia (n=54, 5.3%), pyrexia (n=54, 5.3%), nausea (n=41, 4%), cellulitis (n=37, 3.6%), and cough (n=33, 3.2%). VAERS received 33 reports of death (3.2% of all AE reports for Novavax COVID-19 Vaccine, Adjuvanted). Reports of death were reviewed and none of the deaths were considered causally attributable to vaccination. Of note, FDA requires vaccination providers to report any deaths after COVID-19 vaccination to VAERS, even if it’s unclear whether the vaccine was the cause. Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem. FDA review of U.S. death reports, including review of available medical records and/or autopsy reports, has not identified any new safety concerns.

FDA review of VAERS reports confirms anaphylaxis and myocarditis/pericarditis as known safety concerns, which are included as important identified risks in the current Pharmacovigilance Plan. Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine is included as a contraindication in the Prescribing Information. The Warnings and Precautions section of the Prescribing Information also includes subsections on the Management of Acute Allergic Reactions and on Myocarditis and Pericarditis. No unusual frequency, clusters, or other trends for adverse events were identified from review of VAERS data that would suggest a new safety concern.

Myocarditis/pericarditis

On October 18, 2024, the VAERS database was queried for reports with Preferred Terms (PTs) under the narrow Standardized MedDRA Query (SMQ) "Noninfectious myocarditis/pericarditis" and High Level Term (HLTs) "Noninfectious myocarditis" and "Noninfectious pericarditis." This query returned 40 reports, one of which was excluded as likely a miscoding of an mRNA COVID-19 vaccine report. Of the 39 reports remaining, 12 were serious (excluding otherwise medically important conditions [OMIC]) and none were fatal. Most reports were foreign (n=28) and did not include a vaccination date (n=16). For those reports with a vaccination date, most vaccination dates correlated with

the availability of the Original strain vaccine (n=19). Most reports contained limited clinical information. Only 5 reports included supporting medical records and 2 reports referenced published case reports with detailed clinical descriptions (one of the published articles contained 2 separate cases, bringing the total number of cases to 40). Information on dose number was generally not available or reliable for analysis.

The median age of cases (when reported) was 42 years (range 14 to 83 years). There were 18 female cases and 21 male cases (1 unknown sex). For those cases with precise time to onset reported (n=24), the median time to onset was 9 days (range 0 to 137 days). There was no pattern by lot number (events by lot ranged from 1 to 3). The outcome was reported as recovered in 7 reports, not recovered in 17 reports, and not reported in 15 reports.

The reported diagnosis was pericarditis in 25 cases, myocarditis in 9 cases, and myopericarditis in 6 cases. These counts include 8 cases of recurrent events (6 recurrent pericarditis, 2 recurrent myocarditis). Of these 8 recurrent events, 6 cases had a prior event related to mRNA vaccination and the etiology was unspecified in 2 cases. Finally, after applying the CDC case definitions for myocarditis and pericarditis to the overall 40 retrieved cases, the majority (n=33) did not contain sufficient information to meet the case definition. Among cases that met the CDC case definition, there were 4 cases of pericarditis, 2 cases of myocarditis (probable), and 1 case of myopericarditis (confirmed).

Review of VAERS reports for myocarditis/pericarditis was not suggestive of a new safety signal for this known safety issue.

Atrial Fibrillation and Cerebrovascular Accident

Because the clinical review team noted small numerical imbalances (vaccine vs. placebo) in clinical trial cases of atrial fibrillation and cerebrovascular accident (CVA) during the review (see the Clinical Review Memorandum and final labeling language in 6.1 Clinical Trials Experience section of the USPI), additional VAERS analyses were performed to assess postmarketing cases of atrial fibrillation and CVA following administration of Novavax COVID-19 Vaccine, Adjuvanted. On March 10, 2025, a query of the VAERS database for reports with PTs under the broad SMQ “Supraventricular tachyarrhythmias” returned 16 reports, 14 of which included a reported adverse event of atrial fibrillation. Also on March 10, 2025, a query of the VAERS database for reports with PTs under the HLT “Central nervous system haemorrhages and cerebrovascular accidents” returned 13 reports, all of which included reported adverse events for cerebrovascular accident and one of which also reported atrial fibrillation. Review of VAERS reports returned by these queries was not suggestive of a safety signal for either atrial fibrillation or cerebrovascular accident. For additional details on this analysis, see the Pharmacovigilance Review Memorandum.

Pharmacovigilance Plan

The Applicant’s proposed pharmacovigilance plan (version 3.6, dated March 25, 2025) includes the following important risks and missing information:

- Important identified risks: anaphylaxis, myocarditis and/or pericarditis
- Important potential risks: atrial fibrillation and/or atrial flutter, cerebrovascular accident, cranial nerve VIII disorders (including vestibular neuronitis), 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 [COPD], diabetes, chronic neurological disease, cardiovascular disorders); use in patients with autoimmune or inflammatory disorders; interaction with other vaccines; and long-term safety.

In addition to routine pharmacovigilance, the Applicant agreed to expedite reporting to VAERS (within 15 days of receipt, regardless of seriousness) for the first three years of licensure for the following adverse events: myocarditis and/or pericarditis, atrial fibrillation and/or atrial flutter, cerebrovascular accident, cranial nerve VIII disorders (including vestibular neuronitis), ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI), cardiac failure, and cardiomyopathy. The Applicant will also conduct the postmarketing studies as postmarketing requirements and commitments as listed in Section 10c Recommendation for Postmarketing Activities. Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 10c are adequate to monitor the postmarketing safety for NUVAXOVID (COVID-19 Vaccine, Adjuvanted).

7. Labeling

The proposed proprietary name NUVAXOVID was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 27, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 5, 2024.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed United States Prescribing Information (USPI) and carton and container labels on February 20, 2025, and found them acceptable from a promotional and comprehension perspective.

The review team negotiated revisions to the USPI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant. The USPI and FDA-approved patient labeling submitted in amendment 108 on April 1, 2025, and the carton and container labels submitted in amendment 90 on March 13, 2025, were considered final for approval.

8. Advisory Committee Meeting

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held for this application, as there were no issues or concerns that presented during the course of review of the application that required consult from the advisory committee.

9. Other Relevant Regulatory Issues

In the April 1, 2024, BLA submission, Novavax requested a (b) (4)

10. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of NUVAXOVID (COVID-19 Vaccine, Adjuvanted) that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk-benefit assessment for NUVAXOVID (COVID-19 Vaccine, Adjuvanted) is favorable and supports approval for use in individuals 12 years of age and older.

c. Recommendation for Postmarketing Activities

Required Pediatric Assessments

Under PREA, Novavax, Inc. is required to conduct the following postmarketing activities; these are included in the approval letter.

1. Deferred pediatric study under PREA (Study 2019nCoV-503) to evaluate the safety and immunogenicity of NUVAXOVID in COVID-19 vaccine-naïve individuals 6 months to <12 years of age.
   Final Protocol Submission: March 28, 2022 (Submitted)
   Study Completion: October 28, 2025
   Final Report Submission: March 4, 2026

2. Deferred pediatric study under PREA (Study 2019nCoV-317) to evaluate the immunogenicity of NUVAXOVID in COVID-19 vaccine-naïve seropositive individuals 2 years to <12 years of age and to evaluate the safety and immunogenicity of NUVAXOVID in individuals 6 months to <2 years of age, using a contemporaneously vaccinated comparator group.
   Final Protocol Submission: April 30, 2025
   Study Completion: December 31, 2027
   Final Report Submission: July 31, 2028

3. Deferred pediatric study under PREA (Study 2019nCoV-506) to evaluate the safety and immunogenicity of NUVAXOVID in COVID-19 vaccine-naïve individuals 0 to <6 months of age.
   Final Protocol Submission: October 30, 2028
   Study Completion: March 31, 2031
   Final Report Submission: October 31, 2031

Postmarketing Requirements Under Section 505(O)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct

postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that Novavax is required to conduct the following studies:

4. Study 2019nCoV-402, entitled “Safety of the Novavax COVID-19 vaccine in England using a self-controlled case series design: A post-authorization safety study using data from the Clinical Practice Research Datalink (CPRD) Aurum and linked databases” to evaluate the occurrence of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: March 30, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: June 30, 2028

5. Study 2019nCoV-404, entitled "Safety Profile of the Novavax COVID-19 Vaccine, Adjuvanted in Individuals ≥ 12 Years of Age in the United States" to evaluate the occurrence of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: June 29, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: September 30, 2028

6. Study 2019nCoV-418, entitled “Post-Authorization Safety Study to Evaluate Long-Term Sequalae of Myocarditis and Pericarditis Following Vaccination” to evaluate long-term sequelae of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID with at least 5 years of follow-up.

   Final Protocol Submission: January 31, 2026
   Study Completion Date: December 31, 2031
   Final Report Submission: September 30, 2032

Novavax, Inc. has committed to conduct the following postmarketing activities, which will be included in the approval letter.

<u>Postmarketing Commitments Subject To Reporting Requirements Under Section 506b</u>

7. Study 2019nCoV-405, entitled “Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-

VIPER)" to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

Final Protocol Submission: March 30, 2022 (Submitted)
Study Completion: February 28, 2027
Final Report Submission: June 30, 2027

8. Study 2019nCoV-402, entitled "Safety of the Novavax COVID-19 vaccine in England using a self-controlled case series design: A post-authorization safety study using data from the Clinical Practice Research Datalink (CPRD) Aurum and linked databases" to evaluate the occurrence of atrial fibrillation and cerebrovascular accident following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: March 30, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: June 30, 2028

9. Study 2019nCoV-404, entitled "Safety Profile of the Novavax COVID-19 Vaccine, Adjuvanted in Individuals ≥ 12 Years of Age in the United States" to evaluate the occurrence of atrial fibrillation and cerebrovascular accident following administration of Novavax COVID-19 Vaccine, Adjuvanted or NUVAXOVID.

   Final Protocol Submission: June 29, 2022 (Submitted)
   Study Completion Date: September 30, 2027
   Final Report Submission: September 30, 2028

<u>Postmarketing Commitments Not Subject To The Reporting Requirements Under Section 506b</u>

To conduct a study entitled "Shipping Evaluation of SARS-CoV-2 rS (JN.1 Vaccine) Drug Product in PFS Finished Good Presentation at SIIPL" to provide objective evidence that the SARS-CoV-2 rS JN.1 Variant DP PFS finished goods presentation will maintain its quality after being exposed to shipping and distribution loads between SIIPL and destination sites, including distributors and end users.

Final Report Submission: July 31, 2025

11. References

1. Centers for Disease Control and Prevention. *COVID-19: About COVID-19*. 2024 October 18, 2024]; Available from: https://www.cdc.gov/covid/about/index.html.

2. Centers for Disease Control and Prevention. *CDC Museum COVID-19 Timeline*. 2023 October 18, 2024]; Available from: https://www.cdc.gov/museum/timeline/covid19.html

3. World Health Organization. *WHO COVID-19 dashboard*. 2024 October 18, 2024]; Available from: https://data.who.int/dashboards/covid19/cases?n=o.