U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
(b) (6)

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From:	(b) (6) CBER, FDA
To:	(b) (6) Office of Vaccine Research and Review
Through:	(b) (6) (b) (6) , CBER, FDA
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Novavax, Inc.
Product:	NUVAXOVID (COVID-19 Vaccine, Adjuvanted)[1]
Application Type / Number	BLA 125817/0
Proposed Indication	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
Submission Date:	April 1, 2024
Action Due Date:	April 1, 2025

[1] Also referred to as Novavax COVID-19 Vaccine, Adjuvanted. This memo also references the following formulations: Original strain (NVX-CoV2373; prototype Wuhan strain); 2023 – 2024 formulation (NVX-CoV2601; XBB.1.5 strain); and 2024 – 2025 formulation (NVX-CoV2705; JN.1 strain).

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the Sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125817/0 based on the safety profile of NUVAXOVID. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for NUVAXOVID, should the indication for this product be approved. Please refer to the Appendix for a complete list of materials reviewed for this memorandum.

2 BACKGROUND

Coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus [1]. SARS-CoV-2 infection can be asymptomatic or result in respiratory symptoms that range in severity from mild to severe. Certain populations, including older adults, immunocompromised individuals, and those with chronic conditions or disabilities are at increased risk for severe infection [2].

COVID-19 first emerged in Wuhan, China in late 2019 and rapidly resulted in a global pandemic [3]. As of October 18, 2024, COVID-19 had infected more than 776 million people worldwide resulting in more than 7 million deaths [4]. As of June 1, 2024, nearly 1.2 million people in the U.S. had died of COVID-19 [1].

On December 11, 2020, the FDA issued the first EUA for a COVID-19 vaccine, the Pfizer-BioNTech COVID-19 vaccine, which was soon followed by an EUA for the Moderna COVID-19 vaccine (December 18, 2020) and later the Janssen COVID-19 vaccine (February 27, 2021) [3]. More than a year later, the Novavax COVID-19 Vaccine, Adjuvanted became the final COVID-19 vaccine available under EUA in the US (July 13, 2022) [5]. Lastly, on June 1, 2023, the Janssen COVID-19 vaccine EUA was revoked after the manufacturer requested voluntary withdrawal of the EUA [6].

Since their initial rollout, COVID-19 vaccines have been credited with saving millions of lives both in the US and globally [7-9]. Although both the US and global public health emergencies have been declared over, the SARS-CoV-2 virus continues to circulate, and new variants continue to emerge. For this reason, ongoing access to updated COVID-19 vaccines to match circulating strains of SARS-CoV-2 remains a public health priority [10, 11].

3 PRODUCT INFORMATION

3.1 Product Description

Section 11 of the proposed United States Prescribing Information (USPI) (BLA 125817/0.95) includes the following description:

NUVAXOVID (2024 – 2025 Formula) (COVID-19 Vaccine, Adjuvanted) is a colorless to slightly yellow, clear to mildly opalescent sterile suspension for intramuscular use that is free from visible particles. Each 0.5 mL dose of NUVAXOVID (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.

Section 12 of the proposed USPI (BLA 125817/0.95) describes the mechanism of action as follows:

NUVAXOVID (2024 – 2025 Formula) contains purified, full-length recombinant spike protein. The vaccine elicits an immune response to the recombinant spike protein, which protects against COVID-19.

3.2 Authorized Indication

The current indication from the Emergency Use Authorization (EUA) Fact Sheet for Healthcare Providers (dated August 30, 2024) is provided below:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) 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.

3.3 Proposed Indication

Section 1 of the proposed USPI (BLA 125817/0.95) describes the indication as follows:

NUVAXOVID (2024 – 2025 Formula) 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.

Reviewer comment: (b) (6) *defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the Sponsor for the final agreed-upon indication after FDA review.*

4 PERTINENT REGULATORY HISTORY

- The Novavax COVID-19 Vaccine, Adjuvanted (NVX-CoV2373, sponsored by Novavax, Inc.) was first authorized worldwide on December 20, 2021, in the European Union.
- On July 13, 2022, the FDA issued an Emergency Use Authorization (EUA) for use of the Novavax COVID-19 Vaccine, Adjuvanted in adults (primary series).
- On August 19, 2022, the FDA issued an EUA for use of the Novavax COVID-19 Vaccine, Adjuvanted in adolescents aged 12 through 17 years (primary series).

- On September 12, 2022, the FDA reissued the EUA Letter of Authorization to revise the conditions of authorization related to Vaccine Adverse Event Reporting System (VAERS) reporting requirements for vaccination providers and Novavax, Inc. to include myocarditis and pericarditis.
- On October 19, 2022, the FDA issued an EUA for use of the Novavax COVID-19 Vaccine, Adjuvanted as a first booster dose in certain individuals aged 18 years of age and older.
- On May 11, 2023, the FDA reissued the EUA Letter of Authorization with revisions to Condition G to require the inclusion of distribution data for Novavax COVID-19 Vaccine, Adjuvanted in the monthly periodic safety reports.
- On October 3, 2023, the FDA reissued the EUA Letter of Authorization to authorize the use of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) to prevent COVID-19 in individuals 12 years of age and older.
- On August 30, 2024, the FDA reissued the EUA Letter of Authorization to authorize the use of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) to prevent COVID-19 in individuals 12 years of age and older.
- On April 1, 2024, the Sponsor submitted the final roll of the rolling original BLA submission 125817/0.
- On May 30, 2024, FDA sent the Sponsor a filing notification letter for this original BLA submission, with a review classification for the application of “Standard” and a review goal date of April 1, 2025.

5 DESCRIPTION OF NOVAVAX COVID-19 VACCINE, ADJUVANTED CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed in this memo are primarily from the Integrated Summary of Safety and the Summary of Clinical Safety submitted to BLA 125817/0.4. During review of the original BLA, the Sponsor submitted multiple updated clinical datasets. (b) (6) defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the Sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125817/0 be approved. Please refer to the package insert for the final clinical safety data.

The Sponsor references safety data from multiple clinical studies in this BLA submission. However, (b) (4) drug substances were used in these clinical studies—one produced at a (b) (4) scale (Emergent Manufacturing Operations, Baltimore, Maryland) and one produced at a (b) (4) scale (Fujifilm Diosynth Biotechnologies, Research Triangle Park, North Carolina and Serum Institute of India, Pune, India). The drug substance produced at the (b) (4) scale is considered consistent with the commercial product. Therefore, the Sponsor considers studies using the (b) (4) drug

substance to be “primary studies” and studies using the (b) (4) scale to be “supportive studies” for assessing the safety of Novavax COVID-19 Vaccine, Adjuvanted.[2]

Primary Clinical Studies
The “primary” clinical studies submitted to this BLA (Table 1) include 1) Study 2019nCoV-301, the adult main study and pediatric expansion study comparing NVX-CoV2373 to placebo in the US and Mexico, 2) Study 2019nCoV-307, a lot-to-lot consistency study of NVX-CoV2373, and 3) Study 2019nCoV-311 (Part 1 and Part 2), a study evaluating Omicron subvariant vaccines in adults in Australia.

Study 2019nCoV-301
Study 2019nCoV-301 is an ongoing, Phase 3, randomized (2:1), observer-blinded, placebo-controlled study to evaluate the efficacy, immunogenicity, and safety of NVX-CoV2373 in adult participants ≥ 18 years of age in the US and Mexico, with a pediatric expansion to include adolescents (12 to < 18 years) in the US only. During the “initial vaccination period,” subjects received a 2-dose series (two intramuscular injections 21 days apart) of either NVX-CoV2373 or placebo. After accrual of sufficient follow up time to support application for EUA, subjects then received an additional two injections of the alternate study material during the “blinded crossover period.” Finally, subjects who remained in study follow-up were offered a booster injection of NVX-CoV2373 during the “open-label single booster vaccination period.” Assessment of adverse events (AEs) included collection of reactogenicity data for 7 days following each injection (except during the blinded crossover period), unsolicited treatment emergent AEs (TEAEs) and medically attended adverse events (MAAEs) through 28 days, and vaccine-related MAAEs, adverse events of special interest (AESIs), and SAEs through the end of study (EoS).

Study 2019nCoV-307
Study 2019nCoV-307 is a completed, Phase 3, randomized (1:1:1), observer-blinded study to compare the immunogenicity and safety of three lots of NVX-CoV2373 in previously vaccinated adults in the US. Subjects received a single intramuscular dose of NVX-CoV2373 from one of three different lots. Assessment of AEs included MAAEs and AESIs through 28 days and SAEs through the EoS.

Study 2019nCoV-311 (Part 1 and Part 2)
Study 2019nCoV-311 is a completed, multi-part, Phase 3, randomized (1:1 and 1:1:1), observer-blinded study evaluating the safety and immunogenicity of Omicron subvariant vaccines in adults in Australia previously vaccinated with other COVID-19 vaccines (Moderna and/or Pfizer-BioNTech COVID-19 vaccines). Part 1 evaluated a single booster dose of the Omicron BA.1 subvariant vaccine (NVX-CoV2515) alone, the

[2] Although not considered a primary study, the drug substance used in the “Evaluating COVID-19 Vaccinations Boosters” (COV-BOOST) study was also produced at the (b) (4) scale. COV-BOOST is a UK-funded, phase 2 study of several different COVID-19 vaccines. Data from COV-BOOST were initially referenced in the draft USPI (BLA 125817/0.64) but were not included in the ISS and no clinical study report was submitted. References to COV-BOOST were later removed from the draft USPI (BLA 125817/0.95).

prototype Novavax vaccine (NVX-CoV2373) alone, or a bivalent vaccine containing the prototype and subvariant vaccines (NVX-CoV2515 + NVX-CoV2373). Part 2 evaluated two booster doses of the Omicron BA.5 subvariant vaccine (NVX-CoV2540) alone, the prototype Novavax vaccine (NVX-CoV2373) alone, or a bivalent vaccine containing the prototype and subvariant vaccines (NVX-CoV2540 + NVX-CoV2373). Assessment of AEs included collection of reactogenicity data for 7 days following each injection, unsolicited AEs and MAAEs through 28 days, and vaccine-related MAAEs, AESIs, and SAEs through the EoS.

Table 1. Primary clinical studies of NVX-CoV2373 included in the ISS*

Study	Age/Country	Study Objectives	NVX-CoV2373‡	Placebo‡
2019nCoV-301 (Adult main study) Ongoing DCO 8/18/2022	18 years of age and older US/Mexico	Efficacy Immunogenicity Safety	19,735	9,847
2019nCoV-301 (Pediatric expansion) Ongoing DCO 8/6/2022	12 – 17 years US	Effectiveness Efficacy Immunogenicity Safety	1,487	745
2019nCoV-307 Completed DCO 8/24/2022	18 – 49 years US	Immunogenicity (Lot-to-lot consistency) Safety	824	N/A
2019nCoV-311 (Part 1) Completed DCO 5/22/23	18 – 64 years Australia	Immunogenicity Safety	334 (Group B and Group D)	N/A
2019nCoV-311 (Part 2) † Completed DCO 5/31/2023	18 years of age and older Australia	Immunogenicity Safety	251 (Group G)	N/A

Abbreviations: data cutoff (DCO), United States (US)
*Adapted from Table 1, Integrated Summary of Safety, Module 5.3.5.3, BLA 125817/0.4.
†Study 2019nCoV-311 (Part 2) was ongoing at the time of the ISS.
‡Number of participants who received study vaccine at the start of each clinical study. Numbers reported in the ISS may differ from final counts included in the final agreed-upon USPI.

Supportive Clinical Studies

The “supportive” clinical studies submitted to this BLA include 1) Study 2019nCoV-101 (Part 1), a completed Phase 1, first-in-human, randomized, observer-blinded placebo-controlled study of safety and immunogenicity of 5-µg and 25-µg doses of SARS-CoV-2 rS with or without 50 µg Matrix-M adjuvant in adults in Australia, 2) Study 2019nCoV-

101 (Part 2), a completed[3] Phase 2, randomized, observer-blinded, placebo-controlled study of safety and immunogenicity in adults in Australia and the US, 3) Study 2019nCoV-302, a completed Phase 3, randomized, observer-blinded, placebo-controlled study of efficacy and safety of NVX-CoV2373 in adults in the United Kingdom (UK), and 4) Study 2019nCoV-501, a completed Phase 2a/b, randomized, observer-blinded, placebo-controlled study of efficacy, immunogenicity, and safety in adults in South Africa (including a subset of subjects living with HIV).

Integrated Summary of Safety

The Integrated Summary of Safety (ISS), submitted to BLA 125817/0.4, includes analysis of pooled safety data from both the primary and supportive clinical studies. The following analysis sets were included in the ISS:

- Primary Analysis Set (Study 2019nCoV-301)
- Primary ISS Analysis Set (Studies 2019nCoV-301, 2019nCoV-307, and 2019nCoV-311 [Part 1 and Part 2])
- Supportive ISS Analysis Set (Studies 2019nCoV-101 [Part 1 and Part 2], 2019nCoV-302, and 2019nCoV-501)
- Overall Analysis Set (all primary and supportive studies)

Although safety data from the supportive clinical studies was reviewed as part of the Integrated Summary of Safety, the focus of this review is on the Primary ISS Analysis Set, since this includes the primary studies referenced in the proposed US Package Insert (BLA 125817/0.95).

Adverse events (AEs) in the Primary ISS Analysis Set included solicited AEs[4], unsolicited AEs, medically attended adverse events (MAAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and significant AEs. In addition, AEs in the ISS were evaluated separately for each vaccination period:

- Pre-crossover Primary Series Vaccination Period
- Post-Crossover Primary Series Vaccination Period
- Combined Pre- and Post-Crossover Primary Series Vaccination Period
- Homologous/Heterologous Booster Vaccination period

Reviewer comment: The clinical safety data submitted in support of this BLA are derived from several large, phase 3 randomized clinical trials with diverse study populations and adequate follow-up time since vaccination. In addition, safety data were analyzed by vaccination period, which allows for assessment of how AEs vary by dose number. Safety data from post-crossover and booster vaccination periods present challenges with interpreting causality due to prior exposure to vaccine/placebo and lack of a control group, respectively.

[3] Study 2019nCoV-101 (Part 2) was ongoing at the time of the ISS.
[4] Except for Study 2019nCoV-307, which did not assess solicited AEs.

5.2 Adverse events

Note: This section refers to safety data from the Primary ISS Analysis Set, unless otherwise specified.

Most common AEs

Solicited AEs included injection site reactions (pain/tenderness, erythema [redness], swelling) and solicited systemic reactions (fever, malaise/fatigue, arthralgia [joint pain], myalgia [muscle pain], headache, and nausea/vomiting). Solicited AEs were assessed on post-vaccination Days 0-6 during the pre-crossover primary series vaccination period and the homologous/heterologous booster vaccination period, but not during the post-crossover primary series vaccination period.

Overall solicited injection-site AEs following NVX-CoV2373 were more common after Dose 2 (74.5%) compared to Dose 1 (57.9%) in the primary series vaccination period. Solicited injection-site AEs were slightly lower after booster vaccination (72.7%) than after Dose 2 but still higher compared to Dose 1. The most common solicited injection-site AE in the pre-crossover primary series vaccination period was pain/tenderness (57.7% after Dose 1, 74.3% after Dose 2). Similarly, the most common solicited injection-site AE after booster vaccination was pain/tenderness (72.3%, 68.7%, 72.2%, respectively in each study). Most solicited injection-site AEs were grade 1 or grade 2 reactions.

Overall solicited systemic AEs following NVX-CoV2373 were more common after Dose 2 (68.9%) compared to Dose 1 (48.2%) in the primary series vaccination period. Solicited systemic AEs after booster vaccination (69.4%) were similar to solicited systemic AEs after Dose 2 and higher compared to Dose 1. The most common solicited systemic AE in the pre-crossover primary series vaccination period was fatigue/malaise (29.9% after Dose 1, 53.6% after Dose 2). Similarly, the most common solicited systemic AE after booster vaccination was pain/tenderness (55.1%, 40.8%, 54.4%, respectively in each study). Most solicited systemic AEs were grade 1 or grade 2 reactions.

Subgroup analyses of solicited AEs showed that both injection-site AEs and systemic AEs were higher in subjects aged 18 to <65 years (compared to those aged 65 years and older) and in females (compared to males). Solicited AEs were also lower in Black or African American participants compared to other race categories. Overall frequencies of solicited AEs were comparable between subjects of Hispanic or Latino ethnicity compared to subjects who were Not Hispanic or Latino.

Reviewer comment: Consistent with previously reviewed data (see this reviewer's prior Novavax EUA memos), the Novavax COVID-19 vaccine is associated with higher frequencies of solicited AEs compared to placebo, especially after the second dose and solicited AEs are generally mild or moderate in intensity (Grade 1 or 2). Similar trends by age and gender have also been described previously.

Although differences in the frequency of AEs by race were observed in the ISS, these estimates must be interpreted with caution since the number of subjects in most subgroups by race was relatively small compared to the number of White subjects, which leads to imprecision in subgroup analysis estimates. In addition, differences in the distribution of individual underlying characteristics (e.g., age, gender, comorbidities) between subjects in subgroups by race could lead to differences in AE reporting. Finally, these differences in AE reporting do not necessarily translate into differences in vaccine efficacy (VE). For example, according to the Summary of Clinical Efficacy (BLA 125817/0.4), in Study 2019nCoV-301, VE among White subjects was 89.4% compared to 94% among Black or African American participants, despite the lower reported rates of solicited AEs among Black or African American participants compared to White participants in this study.

Deaths

In the Overall ISS Analysis Set, there were 82 deaths reported among adult subjects who had received at least one dose of NVX-CoV2373 (during the initial vaccination period, post-crossover vaccination period, or booster vaccination period), and 12 deaths reported among adult subjects who had received only placebo (during the initial vaccination period). No adolescent subjects died in the Pediatric Expansion of Study 2019nCoV-301. Event rates were similar between study vaccine groups in each of the following vaccination periods: pre-crossover primary series vaccination period, post-crossover primary series vaccination period, and combined pre- and post-crossover primary series vaccination period. The event rate in the homologous/heterologous booster vaccination period (no placebo control) was comparable to event rates in the other vaccination periods.

Although event rates were similar across vaccine groups, deaths were more frequent among participants aged 65 years and older and among Black or African American or Other race subjects (in both the NVX-CoV2373 group and the placebo group).

Review of line listings of deaths showed that reported causes of death included common medical conditions (heart disease, cancer, COVID-19, stroke, chronic obstructive pulmonary disease) as well as accidents, injuries (including suicide and gunshot wounds), and overdose (especially opioids). Review of individual AEs leading to death showed no notable risk differences between study groups in any vaccination period.

Reviewer comment: Review of line listings of deaths did not reveal a pattern in AEs concerning for a safety issue. Review of narratives of deaths did not reveal any cases that this reviewer considered causally related to vaccination. Reported deaths were low (<1%) overall and comparable between study groups. Causes of death generally reflected common causes of death during a similar time period (i.e., heart disease, cancer, accidents/injuries, COVID-19, etc.) [12]. Finally, analysis of narratives for a subset of deaths with only the Preferred Term "Death" (instead of a specific fatal AE) also did not reveal any findings concerning for a causal relationship to vaccination.

Other SAEs
In the Overall ISS Analysis Set, the overall event rates for SAEs were similar among NVX-CoV2373 and placebo recipients during the pre-crossover, post-crossover, and combined pre- and post-crossover vaccination periods.

Vaccine-related SAEs (according to the study investigator) in the NVX-CoV2373 group for the combined pre- and post-crossover vaccination period included headache, nervous system disorder, thrombocytopenia, myocarditis, Basedow's disease, colitis, angioedema, biliary dyskinesia, cholecystitis acute, cholecystitis chronic, pericarditis, peripheral sensorimotor neuropathy, pulmonary embolism, and deep vein thrombosis. Of these, cholecystitis acute was the only vaccine-related SAE reported in more than one participant (n=18 overall, n=2 related). Lastly, of the SAEs considered related by the investigator, the Sponsor considered the following SAEs related: nervous system disorder, colitis, angioedema, and peripheral sensorimotor neuropathy. Although small (<0.10 events per 100 person-years) risk differences were observed for several individual SAEs, no significant differences were observed for vaccine-related SAEs in the combined pre- and post-crossover vaccination period.

In the homologous/heterologous booster vaccination period, the study investigator considered the following SAEs as related to NVX-CoV2373: acute respiratory failure, asthma, pulmonary embolism, acute myocardial infarction, cholecystitis, cellulitis, tendonitis, and deep vein thrombosis. Of these, the Sponsor considered cellulitis to be the only vaccine-related SAE in the booster vaccination period.

Subgroup analyses showed higher rates of SAEs reported among subjects aged 65 years and older compared to subjects aged 18 to <65 years for each vaccination period.

Reviewer comment: Although the investigator considered several SAEs to be related to vaccination, there was no clear pattern or trend in SAEs to suggest a new safety issue.

AESIs

PIMMCs
In the Overall ISS Analysis Set, rates of Potential Immune-Mediated Medical Conditions (PIMMCs) were similar in the pre-crossover vaccination period, higher among placebo to NVX-CoV2373 subjects in the post-crossover vaccination period, and higher in the placebo group in the combined pre- and post-crossover vaccination period. Despite these varying differences by vaccination period, no consistent trends were noted between study groups and no notable risk differences were observed for individual PIMMC AEs. Subgroup analyses showed female subjects with higher rates of PIMMCs than males, but without any consistent differences among NVX-CoV2373 and placebo recipients. For the booster vaccination period, event rates for PIMMCs were comparable to those in the pre- and post-vaccination period.

O/E analysis

As requested by FDA in an Information Request before submission of the BLA, the Sponsor performed observed-to-expected (O/E) analysis of 42 prespecified AESIs (see Table 227 on page 533 of the ISS for AESI list and results). The Sponsor used pooled safety data from the pre- and post-vaccination periods in studies 2019nCoV-101 (Part 1), 2019nCoV-101 (Part 2), 2019nCoV-301 (Adult Main Study), 2019nCoV-302, and 2019nCoV-501. Although O/E ratios were slightly elevated (O/E ratio between 1 and 2) for several AESIs, the only AESI with a statistically significant elevation was myocarditis with a 0-42 day risk window (O/E ratio 11.6, 95% confidence interval [2.4, 33.9]).

Anaphylaxis

There were no vaccine-related SAEs of anaphylactic reaction during any of the study periods. A subject in the Adult Main Study of 2019nCoV-301 experienced an anaphylactic reaction after receiving booster vaccination with NVX-CoV2373, but it was attributed to a previously known food allergy (aged cheese).

Myocarditis/Pericarditis

In Study 2019nCoV-301, myocarditis was reported in one subject (<0.1%) in the NVX-CoV2373 group and myopericarditis was reported in one subject (<0.1%) in the placebo group in the pre-crossover vaccination period. In the post-crossover vaccination period, pericarditis was reported in one subject (<0.1%) in the NVX-CoV2373 to placebo group. In addition, one non-serious event of myocarditis and pericarditis was reported in one subject (<0.1%) in the placebo to NVX-CoV2373 group during the post-crossover vaccination period. In the Pediatric Expansion of Study 2019nCoV-301, one subject (<0.1%) in the placebo to NVX-CoV2373 group reported myocarditis during the post-crossover vaccination period. No cases of myocarditis or pericarditis were reported following a booster in all of Study 2019nCoV-301 (adults and adolescents) as well as in the Overall Analysis Set.

Analysis of event rates in the Overall Analysis Set showed comparable rates of myocarditis and pericarditis between NVX-CoV2373 and placebo recipients, with no significant risk differences observed. However, as mentioned previously, observed-to-expected analysis demonstrated a statistically significant elevation for myocarditis within 42 days of receipt of NVX-CoV2373.

Reviewer comment: Because the Sponsor submitted multiple updated datasets during review of the original BLA, counts derived from the ISS discussed in this memo may differ from counts in the final agreed-upon USPI. Please refer to the final agreed-upon USPI for final clinical safety data.

Among the various AESIs assessed in the ISS, the only AESI with findings concerning for a safety signal is myocarditis, which is already considered an identified risk. No new safety signals were identified in review of AESI analyses in the ISS.

6 SUMMARY OF POSTMARKETING EXPERIENCE

6.1 Sponsor's Analysis

Since the initial US authorization, the Sponsor submitted monthly Summary Safety Reports (SSRs), reporting interval and cumulative postmarketing safety data for Novavax COVID-19 Vaccine, Adjuvanted, until the FDA requested a change to quarterly reporting, starting with reporting interval August-October 2024.

On November 26, 2024, FDA received SSR #32 (IND 22430.701) for reporting period August 1, 2024 – October 31, 2024. The report includes exposure and safety data for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula), and Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). As of October 31, 2024, there had been limited uptake of Novavax COVID-19 vaccines in the US compared to the rest of the world (Table 2). Although the number of reported administered doses has modestly increased with each iteration of the vaccine in the US, this number has progressively decreased globally. Similarly, the number of globally reported individual case safety reports (ICSRs) and AEs has progressively decreased with each iteration of the vaccine. Lastly, overall reporting rates have also decreased with each iteration of the vaccine (Table 3).

Table 2. Cumulative administration data for Novavax COVID-19 vaccines from post-authorization experience*

Region	Original monovalent	2023-2024 Formula	2024-2025 Formula
US	89,195	248,330	385,129
World	2,935,852	1,212,889	450,391

*Adapted from Table 3, MSSR #32 (IND 22430.701); excludes Covovax doses

Table 3. Cumulative worldwide ICSRs and AEs for Novavax COVID-19 vaccines*

Parameters	Original monovalent	2023-2024 Formula	2024-2025 Formula
Number of ICSRs	5,179	596	85
Serious ICSRs (includes fatal)	1,020	84	13
Non-serious ICSRs	4,159	512	72
Number of AEs	18,482	2,108	262
Serious AEs (includes fatal)	2,894	209	29
Non-serious AEs	15,588	1,899	233
Reporting rate (ICSRs per 100 doses administered)	0.17	0.05	0.02

Abbreviations: individual case safety reports (ICSRs), adverse events (AEs)
*Adapted from Table 4, MSSR #32 (IND 22430.701).

Although numerous safety signals have been investigated by the Sponsor to date, only the following safety signals are currently considered confirmed safety signals:

anaphylaxis, myocarditis and/or pericarditis, and paresthesia.[5] Each of these confirmed safety signals is now described in the label. In addition, anaphylaxis and myocarditis and/or pericarditis are important identified risks in the current pharmacovigilance plan.

Finally, no confirmed safety signals have arisen from the topics for which FDA has requested monitoring in SSRs: cholecystitis, hepatitis and liver injury, potential immune-mediated medical conditions (PIMMC), vaccination errors, and inflammatory eye disorders.

Reviewer comment: Review of findings from SSR #32 did not reveal any new safety signals.

Myocarditis and/or pericarditis

In each SSR, the Sponsor employed both a narrow and broad search strategy to evaluate postmarketing reports of myocarditis and/or pericarditis. The narrow search strategy, which is used for observed-to-expected (O/E) analyses, utilizes the narrow Standardized MedDRA Query (SMQ) Noninfectious myocarditis/pericarditis and HLTs Noninfectious myocarditis and Noninfectious pericarditis. The broad search strategy, which is used for adjudicating cases with Brighton Collaboration criteria, utilizes the broad SMQ Noninfectious myocarditis/pericarditis and HLTs Noninfectious myocarditis, Noninfectious pericarditis, Infectious myocarditis, and Infectious pericarditis.

Using the narrow search strategy, the Sponsor retrieved 96 ICSRs for myocarditis and/or pericarditis, the majority of which (n=89) were associated with the Original strain vaccine. Observed-to-expected analysis of these unadjudicated cases showed that O/E rates for all vaccine formulations combined were significantly greater than expected for risk windows 0-7 days and 0-14 days. When stratified by age and sex, O/E rates for all vaccine formulations combined were significantly greater than expected for males aged 0-19 years, males aged 20-29 years, females aged 20-49 years, and females overall.

When limiting to cases of myocarditis (n=33 ICSRs for all vaccines combined), O/E rates were significantly greater than expected for all risk windows (0-7, 0-14, 0-30, and 0-42 days). When stratified by age and sex (myocarditis cases only), O/E rates for all vaccine formulations combined were significantly greater than expected for males aged 0-19 years, males overall, females aged 20-29 years, and females overall.

When limiting to cases of pericarditis (n=61 ICSRs for all vaccines combined), O/E rates for all vaccine formulations combined were significantly greater than expected for risk windows 0-7 days and 0-14 days. When stratified by age and sex (pericarditis cases only), no statistically significantly increased O/E rates were observed.

[5] Tinnitus was initially confirmed by the Sponsor but later refuted. Of note, FDA disagreed with the Sponsor's initial assessment and proposal to include "Tinnitus" in the USPI during review of the 2023-2024 Formula (see this reviewer's Pharmacovigilance EUA Amendment Memorandum for the 2023-2024 Formula for additional details).

Using the broad search strategy, the Sponsor retrieved 154 ICSRs, of which 53 met Brighton Collaboration case definitions for myocarditis and/or pericarditis (Level 1-3). Most (n=52) of these "confirmed" cases were following the Novavax COVID-19 Vaccine, Adjuvanted (Original strain); one case was following the 2024-2025 Formula vaccine. Myocarditis (n=31 instances) was reported more often than pericarditis (n=26 instances) among confirmed cases (although some cases reported both myocarditis and pericarditis). There were more confirmed cases among females (n=30) than males (n=23) and represented age groups ranged from 18 to 60+ years without an obvious pattern or clustering by age or sex. Time to onset was most often reported as 0-7 days (n=26), followed by 8-14 days (n=9), then greater than 15 days (n=7). Ten cases had unknown time to onset. Outcomes were reported as follows: Not Recovered (n=22), Unknown (n=23), Recovering (n=9), Recovered (n=5), Recovered with sequelae (n=2).

Reviewer comment: Although O/E analyses demonstrate an elevated rate of myocarditis and/or pericarditis up to 42 days post-vaccination (depending on the AE and vaccine formulation), data from stratified analyses become sparse, with no clear discernable pattern of risk based on age or sex. Although most adjudicated cases are reported to occur within 0-7 or 0-14 days of vaccination, a substantial number of adjudicated cases occurred after 15 days or with unknown time to onset. Finally, long-term outcomes from adjudicated cases are largely unknown/not reported.

Anaphylaxis

In each SSR, the Sponsor performed O/E analyses to evaluate postmarketing reports of anaphylaxis following Novavax COVID-19 vaccination. As of SSR #32, of the 75 ICSRs reported cumulatively, 72 AEs met inclusion criteria for the unadjudicated O/E analyses with a risk window of 0-7 days. Results of the unadjudicated O/E analyses showed a significantly elevated O/E ratio for all risk windows (0-1, 0-2, and 0-7 days). For age/sex stratifications, the O/E results remained elevated for the males overall, males aged 20-29 years, males aged 40-49 years, females aged 0-69 years, and females overall. In addition, the Sponsor performed adjudicated analyses by applying the Brighton Collaboration case definition for anaphylaxis. Fourteen cases met Brighton Collaboration criteria (Level 1-3) for anaphylaxis. O/E analysis of confirmed cases showed that O/E rates remained significantly elevated for the 0-1 day risk window.

Reviewer comment: Although O/E analyses for anaphylaxis demonstrate an elevated rate of anaphylaxis for all risk windows, most cases fell within the 0-1 day risk window, which also had the highest O/E ratio of all risk windows. When stratified by age/sex, a stronger relationship was observed for females than males, as the majority of the 72 AEs (n=60) were among females. This is consistent with prior publications with VAERS data, which show that the majority of spontaneously reported cases of anaphylaxis are among female vaccine recipients [13, 14].

6.2 FDA Analysis

6.2.1 VAERS Reports

This reviewer queried the VAERS database on October 18, 2024, for all VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent, 2023-2024 Formula, and 2024-2025 Formula) since initial US authorization (July 13, 2022).

Total VAERS event counts were low (Table 4) compared to worldwide ICSR counts reported by the Sponsor (Table 3). Monthly VAERS event counts (overall and serious) had been trending down since February 2023, with a modest increase in overall reporting after the authorization of the 2024-2025 Formula.

Table 4. Novavax vaccine VAERS event counts by location and seriousness

	All	Serious	Deaths
US	589	131	6
Foreign	428	426	27
Total	1,017	557	33

The 10 most common Preferred Terms (PTs) overall and for serious reports only are displayed in Table 5.[6] (For additional tables on most common PTs in Novavax VAERS reports, see the Appendix).

Table 5. Ten most common PTs in Novavax vaccine VAERS reports, all ages

a) All reports

MedDRA Preferred Term	Count (n)	Rank
Headache	123	1
Dizziness	113	2
Fatigue	99	3
Pyrexia	91	4
Chest pain	84	5
Dyspnoea	80	6
Myalgia	77	7
Nausea	77	7
Pain	68	9
Pain in extremity	59	10

b) Serious reports

MedDRA Preferred Term	Count (n)	Rank
Headache	71	1
Chest pain	61	2
Dyspnoea	58	3
Dizziness	57	4
Fatigue	54	5
Myalgia	54	5
Pyrexia	54	5
Nausea	41	8
Cellulitis	37	9
Cough	33	10
COVID-19	33	10

Reviewer comment: Review of the most common PTs (overall and serious only) shows that most PTs are either labeled AEs (headache, fatigue, pyrexia, myalgia, nausea), related to labeled AEs (pain, pain in extremity), confounding by indication (COVID-19),

[6] Tables in this memo that display most common PTs are based on derived events-based data (i.e., when VAERS reports from multiple reporters involving one individual are combined into a single case). Events-based VAERS data is intended for adverse event screening purposes. While generally representative of the underlying source data, there can be discrepancies when compared to the source VAERS reports. Additional review of reported source data may be warranted.

or non-specific symptoms for which further evaluation of reports was either related to labeled AEs or not suggestive of a safety signal for a specific diagnosis (dizziness, chest pain, dyspnea). Review of death reports did not identify any fatalities that this reviewer considered causally attributable to Novavax vaccination. Death reports generally lacked sufficient information to make an adequate assessment of causality or were confounded by underlying comorbidities or conditions. Throughout the post-authorization surveillance period, this reviewer has investigated multiple PTs for potential safety signals. However, no new confirmed safety signals have arisen, aside from the confirmed safety signals of anaphylaxis, myocarditis and/or pericarditis, and paresthesia.

Pregnant and breastfeeding

Among the 1,017 VAERS events overall, 12 (0.01%) included PTs under the System Organ Class (SOC) Pregnancy, Puerperium and Perinatal conditions. PTs with more than one VAERS event included Exposure during pregnancy (n=4), Maternal exposure during pregnancy (n=4), Foetal exposure during pregnancy (n=2), Large for dates baby (n=2), and Pre-eclampsia (n=2). Review of individual VAERS reports was not suggestive of a pattern of AEs concerning for a safety signal. In addition, individual reports contained insufficient information to draw conclusions regarding causality, as many lacked sufficient clinical details or contained confounding factors (e.g., advanced maternal age, increased maternal body mass index [BMI], concomitant medications and vaccines, and alcohol use).

Adolescents aged 12 to <18 years

A separate query for individuals aged 12 to <18 years returned 20 events, one of which was serious. The most common PTs (4 or more instances) were Loss of consciousness (n=6), Dizziness (n=5), Chest pain (n=4), Headache (n=4), Pallor (n=4), Syncope (n=4), and Unresponsive to stimuli (n=4). The one serious event (VAERS ID #2727402-1) involved a 14-year-old male who received dose 2 of the Novavax vaccine (along with multiple other concomitant vaccinations) and 9 days later developed pericarditis, chest pain, and headache. He went to an emergency department and was evaluated by a cardiologist. The outcome at the time of reporting was unknown.

Reviewer comment: Review of the limited number of VAERS reports for adolescents showed that the most common AEs were related to episodes of syncope. Syncope is a labeled event for Novavax vaccine and is considered a common AE following immunization for adolescents in general [15]. In addition to the serious report of pericarditis, there is a nonserious report of pericarditis that is likely regarding the same patient (VAERS ID #2708641-1).

Anaphylaxis

A separate query for reports with PTs under the narrow SMQ Anaphylactic reaction returned 29 reports, of which 8 were serious and none were fatal. Most (n=28) reports were foreign and reported anaphylactic or anaphylactoid reaction with a median time to onset (when reported) of 0 days. Most reports were for females (n=18) and the median age (when reported) was 38 years.

Reviewer comment: Anaphylaxis is a known risk for COVID-19 vaccines, including Novavax COVID-19 Vaccine, Adjuvanted. Review of VAERS reports did not reveal any new aspects of this known safety issue to suggest a new safety signal.

Myocarditis and/or pericarditis

A separate query for reports with PTs under the narrow SMQ Noninfectious myocarditis/pericarditis and HLTs Noninfectious myocarditis and Noninfectious pericarditis 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 most reports 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).

Ocular motor cranial nerve disorders

A separate query for reports with PTs under the HLT Eye movement disorders returned 2 reports, both of which were serious and non-fatal. Both reports describe the same event of a 72-year-old woman with a history of diabetes and hypertension who received Novavax COVID-19 Vaccine and later that day developed tearing of the left eye. The next morning, she had difficulty controlling left eye movement and opening the eye lid and experienced double vision. She was hospitalized for three days and diagnosed with 3rd cranial nerve palsy. She also received the Fluad Quadrivalent vaccine approximately 17 days prior to the event. At the time of reporting the outcome was “not recovered/not resolved.”

Reviewer comment: Similar to the two clinical trial cases of ocular motor cranial nerve disorder, this single post-authorization case is confounded by multiple risk factors (advanced age, hypertension, and diabetes). No new safety signal was identified in review of VAERS reports of ocular motor cranial nerve disorder.

Hepatobiliary disorders

A separate query for reports with PTs under the SOC Hepatobiliary disorders returned 4 reports, including reports of autoimmune hepatitis (n=1), liver injury (n=1), hepatic pain (n=1), and gallbladder disorder or colitis (n=1). These reports lacked sufficient information to make an adequate assessment of causality and there was no pattern of AEs concerning for a safety signal.

Reviewer comment: Review of VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted, confirmed the presence of reports for known safety issues (e.g., myocarditis/pericarditis, anaphylaxis) but did not reveal any new safety signals.

Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, 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 actually due to the product.

Addendum: In addition to the VAERS analyses in this section, this reviewer also performed several additional VAERS queries in response to late-breaking queries from the review team. Please see the section 11 "Late-breaking issues addendum" of this memo for these additional VAERS analyses.

6.2.2 Data mining

Data mining for Novavax COVID-19 Vaccine, Adjuvanted was conducted using the Empirica Signal Signals tab "VAERS Summary Table" on October 17, 2024.[7] The data lock point was October 11, 2024. The PTs with an EB05≥2 are shaded in red in the table below.

Table 6. Data mining results for Novavax vaccine

PT	World EB05	US EB05	US Adult1* EB05
Anaphylactoid reaction	21.959		
Antibody-dependent enhancement	19.706		
Breakthrough COVID-19	6.035	5.079	0.562

[7] The minimum standard analysis is the "VAERS Summary Table" in the signal management application. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock date listed. The background database contains VAERS reports since 1990. Adjusting for age, sex, and year, EB data mining generates ratios of observed-to-expected counts [Empirical Bayes Geometric Mean (EBGM)] for vaccine-adverse event combinations. Results greater than two for the lower bound of the 90% confidence interval for the EBGM (i.e., EB05 > 2) are considered statistics of disproportionate reporting.

COVID-19 immunisation	1.403	2.017	0.556
Cellulitis	10.257		
Chest pain	2.555	1.407	1.326
Dizziness	1.752	1.804	2.207
Heart rate increased	1.21	1.374	2.036
Interchange of vaccine products	0.85	2.082	0.771
Laryngospasm	2.889		
Paralysis	2.789	0.485	
Pericarditis	2.526	1.454	0.502

*Adult1: 19-<45 years

Reviewer comment: This reviewer has evaluated data mining results for Novavax vaccine throughout the post-authorization surveillance period. No new safety issues are represented in these data mining results. PTs include labeled AEs (i.e., pericarditis), terms that are related to labeled AEs (i.e., anaphylactoid reaction, laryngospasm), non-specific AEs not suggestive of a specific diagnosis (i.e., chest pain, dizziness, heart rate increased), and terms are not AEs per se (i.e., breakthrough COVID-19, COVID-19 immunisation, incorrect dose administered, interchange of vaccine products). Review of reports for other AEs (i.e., antibody-dependent enhancement, cellulitis, paralysis) was not concerning for a safety signal.

Data mining is subject to a number of limitations including the limits of spontaneous surveillance systems described in the section above. There may be confounding by indication or false alerts from concomitant product administration. In addition, a signal may be reflected in multiple PTs that individually do not reach alert threshold. Data mining findings are subject to a number of potential limitations and are to be regarded as "hypothesis generating." Data mining findings do not imply causality.

7 SPONSOR'S PHARMACOVIGILANCE PLAN

On April 1, 2024, the Sponsor submitted US Pharmacovigilance Plan (PVP) Version 3.2, dated March 14, 2024 (BLA 125817/0.4). An updated PVP (Version 3.3, dated December 3, 2024) was submitted on December 5, 2024 (BLA 125817/0.49). This PVP included a description of routine pharmacovigilance (PV) activities as well as additional PV activities by safety concern. On February 11, 2025 (BLA 125817/0.69), the Sponsor submitted an updated PVP (Version 3.4, dated February 6, 2025). Updates to this PVP include updated postmarketing myocarditis and pericarditis study information in accordance with CBER IR #46 and updated milestones for postmarketing safety studies in accordance with CBER IR #47. Study tables were also updated to reflect the status of Study 2019nCoV-313 (Parts 1 and 2) as completed. On March 19, 2025, in response to CBER IR #72, the Sponsor submitted an updated PVP (Version 3.5, submitted to BLA 125817/0.98). Updates to this PVP included the addition of important potential risks (atrial fibrillation and/or atrial flutter, cerebrovascular accident, and cranial nerve VIII disorders [including vestibular neuronitis]) in accordance with CBER IR #72. In addition, the Sponsor changed the date of the next interim report for Study 2019nCoV-402 to September 30, 2025, to accommodate the addition of new study outcomes. On March 26, 2025, in response to CBER IR #77, the Sponsor submitted an updated PVP (Version 3.6, submitted to BLA 125817/0.102).

Routine PV includes adverse event (AE) reporting, signal detection, and targeted AE follow-up questionnaires for Important Identified Risks “Anaphylaxis” and “Myocarditis and/or pericarditis.” Signal detection activities include both qualitative and quantitative methods performed on a monthly basis, including evaluation of data from Novavax’s Global Vaccine Safety Database, the EudraVigilance Data Analysis System (EVDAS), the Vaccine Adverse Event Reporting System (VAERS), information from health authorities, and the medical literature. A prespecified list of Adverse Events of Special Interest (AESI) will be evaluated on an interval and cumulative basis, with observed-to-expected analysis planned for validated signals for AESI with established case definitions and background rates. For aggregate reporting, periodic safety reports will be submitted quarterly for the first three years post-approval, then annually thereafter. Additional PV activities include one ongoing clinical trial, five ongoing observational studies, and one planned observational study (to evaluate long-term sequelae of myocarditis and pericarditis following vaccination). Additional PV activities by safety concern are summarized in Table 8 below.

Table 8. Sponsor’s Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	Anaphylaxis	Routine PV Targeted follow-up questionnaire Ongoing clinical trial • Study 2019nCoV-301 Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Identified Risk	Myocarditis and/or pericarditis	Routine PV Targeted follow-up questionnaire Expedited reporting Ongoing clinical trial • Study 2019nCoV-301 Post-authorization studies • 2019nCoV-404 • 2019nCoV-402 • 2019nCoV-418
Important Potential Risk	Atrial fibrillation and/or atrial flutter	Routine PV Expedited reporting Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Potential Risk	Cerebrovascular accident	Routine PV Expedited reporting Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Potential Risk	Cranial nerve VIII disorders (including vestibular neuronitis)	Routine PV Expedited reporting Post-authorization studies • 2019nCoV-404 • 2019nCoV-402

Important Potential Risk	Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)	Routine PV Expedited reporting Ongoing clinical trial • Study 2019nCoV-301 Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Missing Information	Use in pregnancy and while breastfeeding	Routine PV Post-authorization studies • Study 2019nCoV-405
Important Missing Information	Use in immunocompromised patients	Routine PV Ongoing clinical trial • Study 2019nCoV-301 Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Missing Information	Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)	Routine PV Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Missing Information	Use in patients with autoimmune or inflammatory disorders	Routine PV Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Missing Information	Interaction with other vaccines	Routine PV Post-authorization studies • 2019nCoV-404 • 2019nCoV-402
Important Missing Information	Long-term safety	Routine PV Ongoing clinical trial • Study 2019nCoV-301 Post-authorization studies • 2019nCoV-404 • 2019nCoV-402

*Adapted from Table 3, US Pharmacovigilance Plan (PVP) Version 3.6, dated March 25, 2025, BLA 125817/0.102, Module 1.16.1

7.1 Enhanced Pharmacovigilance

The Sponsor plans to implement specific targeted AE follow-up questionnaires for the following safety concerns:

- Myocarditis and/or pericarditis
- Anaphylaxis

In addition, in response to CBER IR #72, on March 18, 2025 (BLA 125817/0.96), the Sponsor agreed to expedited reporting for the following AEs (regardless of seriousness or expectedness) for the first three years of licensure:

- Myocarditis and/or pericarditis
- Atrial fibrillation
- Cerebrovascular accident

- Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)
- Cranial nerve VIII disorders (including vestibular neuronitis)

Atrial flutter, cardiac failure, and cardiomyopathy were later added to this list and confirmed by the Sponsor in their response submitted to BLA 125817/0.102.

Reviewer comment: Throughout the EUA, the FDA required the Sponsor to adhere to reporting requirements for specific AEs under the Conditions of Authorization. According to the most recent EUA Letter of Authorization (dated August 30, 2024), Condition F requires the following:

F. Novavax, Inc. will report to VAERS:
- *Serious adverse events (irrespective of attribution to vaccination);*
- *Cases of myocarditis;*
- *Cases of pericarditis;*
- *Cases of Multisystem Inflammatory Syndrome; and*
- *Cases of COVID-19 that result in hospitalization or death, that are reported to Novavax, Inc.*

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Novavax, Inc.

In addition to required reporting of these AEs, the Sponsor also agreed to expedited reporting under the EUA for any cases of Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI), which would include any reports with PTs under the HLT "Eye movement disorders" (EUA 28237/0.149).

Expedited reporting for certain AEs (SAEs irrespective of attribution to vaccination, MIS, and COVID-19 resulting in hospitalization or death) is not included in the Sponsor's proposed PVP under the BLA. The decision to not continue expedited reporting of these cases (regardless of seriousness or expectedness) is reasonable given the lack of cases suggestive of a safety signal related to these AEs to date.

7.2 Safety-related Post-marketing Studies

Five ongoing observational studies are listed as additional PV activities to further evaluate the safety and effectiveness of Novavax COVID-19 Vaccine, Adjuvanted in the postmarketing setting (Table 9). Three of these studies are current post-authorization safety studies and two are current post-authorization effectiveness studies, all of which were initiated during the Emergency Use Authorization (EUA) for Novavax COVID-19 Vaccine, Adjuvanted.

The three ongoing post-authorization safety studies and the one planned long-term myocarditis study are briefly described in this section. For a description of the two post-authorization effectiveness studies please see the review memo by the Real-World Evidence reviewer.

Table 9. Ongoing post-authorization studies*

Study	Description
2019nCoV-401	European Real-World Effectiveness Study EU/EEA Post-authorization Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform
2019nCoV-402	UK Active Follow-up for Safety UK Post-authorization Safety Study Using the Clinical Practice Research Datalink (CPRD)
2019nCoV-403	US Real-World Effectiveness Study US Post-authorization Effectiveness Study Using a Claims Database
2019nCoV-404	US Active Follow-up for Safety US Post-authorization Safety Study using a Claims Database
2019nCoV-405	Pregnancy Exposure Registry Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER

Abbreviations: European Union (EU), European Economic Area (EEA), United Kingdom (UK), United States (US)
*Adapted from Tables 5 – 7, 9 – 10, US Pharmacovigilance Plan (PVP) Version 3.6, dated March 25, 2025, BLA 125817/0.102, Module 1.16.1

Reviewer comment: In addition to the five ongoing post-authorization studies, the Sponsor's updated PVP (BLA 125817/0.102) also includes a synopsis of the proposed post-authorization safety study to evaluate long-term sequalae of myocarditis and pericarditis following vaccination. This is discussed in more detail below. Vaccine effectiveness studies are mentioned in this memo for completeness only. (b) (6) *defers to* (b) (6) *and the clinical review team for evaluation of postmarketing vaccine effectiveness studies including determination of their status (i.e., voluntary vs. PMC).*

7.2.1 Study 2019nCoV-402: UK Post-authorization Safety Study Using the Clinical Practice Research Datalink (CPRD)

Note: For a detailed review of the study protocol for Study 2019nCoV-402, see the following review memo:

- *Post-authorization Real-World Evidence Memorandum* (b) (6) *dated June 28, 2022 (Review of protocol version 1.0, dated March 18, 2022, submitted to IND 22430/0.258 on March 30, 2022)*

For updated versions of the protocol, see:

- *Protocol version 2.0, dated March 18, 2022, submitted to IND 22430/0.361 on September 29, 2022 (addresses regulatory agency comments)*

- *BIRAMS comments* (b) (6) *dated November 17, 2023 (Review of protocol version 4.0, dated October 20, 2023, submitted to IND 22430/0.552 on October 26, 2023)*
- *Post-authorization Safety Study Protocol Review Memorandum* (b) (6) *dated September 6, 2024 (Review of protocol version 5.0, dated August 16, 2024, submitted to IND 22430/0.676 on August 27, 2024)*

Study title
Safety of the Novavax COVID-19 vaccine in England using a self-controlled case series design: A post-authorisation safety study using data from the Clinical Practice Research Datalink (CPRD) Aurum and linked databases

Study design
This retrospective, observational study employs both a self-controlled case series study (SCCS) design as well as a matched cohort analysis. Primary and secondary objectives are evaluated using the SCCS study design and exploratory objectives are evaluated using the matched cohort analysis.

Study objective
The primary objective as stated in the protocol is "to evaluate the risk of select AESI following vaccination with at least one dose of Nuvaxovid using an SCCS design" (page 17, protocol v5.0, IND 22430/0.676). Secondary and exploratory objectives are listed on pages 19-29 of the protocol.

Study population
The study population includes individuals aged 12 years and older in the CPRD Aurum database who were registered with a General Practitioner in England and were vaccinated with Nuvaxovid between September 5, 2022, through to an estimated 30 months (2.5 years) after first administration following authorization. The estimated sample size varies depending on the incidence rate for each AESI. For a description of the sample size, see page 33 of the study protocol v5.0.

Data collection
Electronic health record (EHR)-derived data from primary care practices in England provides patient-level data (e.g., diagnoses, prescriptions, etc.) to the CPRD Aurum database for over 13 million patients. This data is then linked to multiple other health-related data sources (e.g., disease registries, death registration records, etc.), which are described in more detail on pages 31-33 of the study protocol v5.0. AESIs will be identified using SNOWMED CT and ICD-10 CM diagnosis codes. See Table 1, pages 16-17 of protocol version 5.0 for a list of AESIs, including clean and risk windows.

Data analysis
The primary objective will be assessed using conditional Poisson regression models to compare incidence rates during risk windows to incidence rates during control windows for each AESI. (Secondary objectives evaluate incidence rate ratios for AESI by dose number and among subgroups of interest). Exploratory objectives will be assessed in

the matched cohort analysis via inverse probability treatment weighting (IPTW) propensity score (PS) analysis to make comparisons between Nuvaxovid recipients and referent groups (recipients of Pfizer COVID-19 vaccine, recipients of Moderna COVID-19 vaccine, and unvaccinated individuals, respectively). In addition, Kaplan-Meier estimates for AESIs will be generated for each cohort and Cox proportional hazards models for matched pairs will be used to compare cohorts for each AESI. Lastly, comparison to unvaccinated individuals will include risk-set sampling (RSS).

Milestone dates

Milestone dates listed in the updated PVP (Version 3.6) are as follows:

- Interim Report Submission: September 30, 2025; June 30, 2026; June 30, 2027
- Study Completion Date: September 30, 2027
- Final Report Submission: June 30, 2028

Interim results

According to the most recently submitted Interim Report (Interim Report #2, submitted to IND 22430/0.651, data cutoff date January 23, 2024), among the more than 15 million individuals included in the source population, 277 (0.002%) received at least one dose of the Nuvaxovid vaccine between September 5, 2022, and January 23, 2024. There were 11 AESI identified in Nuvaxovid recipients, but because the number of Nuvaxovid recipients was too small for analysis, no safety conclusions were drawn.

7.2.2 Study 2019nCoV-404: US Post-authorization Safety Study Using a Claims Database

Note: For a detailed review of the study protocol for Study 2019nCoV-404, see the following review memo:

- *Post-authorization Real-World Evidence Memorandum* (b) (6) *, dated October 7, 2022 (Review of protocol version 1.0, dated June 15, 2022, submitted to IND 22430/0.316 on June 29, 2022)*

For a updated versions of the protocol, see:

- *Protocol version 2.0, dated November 29, 2022, submitted to IND 22430/0.382 on November 30, 2022 (addresses regulatory agency comments)*
- *BIRAMS comments* (b) (6) *dated November 17, 2023 (Review of protocol version 4.0, dated October 20, 2023, submitted to IND 22430/0.552 on October 26, 2023)*
- *Post-authorization Safety Study Protocol Review Memorandum* (b) (6) *dated September 6, 2024 (Review of protocol version 5.0, dated August 16, 2024, submitted to IND 22430/0.676 on August 27, 2024)*

Study title

Safety Profile of the Novavax COVID-19 Vaccine, Adjuvanted in Individuals ≥ 12 Years of Age in the United States

Study design

This retrospective, observational study employs a self-controlled case series study (SCCS) design as well as a cohort study design of individuals in a claims database (HealthVerity's COVID-19 database). Primary and secondary objectives are evaluated using the SCCS study design and exploratory objectives are evaluated using the retrospective cohort study design.

Study objective

The primary objective as stated in the protocol is "to evaluate the risk of select adverse events of special interest (AESIs) following vaccination with at least one dose of a Novavax COVID-19 Vaccine using a self-controlled design" (page 16, protocol 5.0, IND 22430/0.676). Secondary and exploratory objectives are listed on pages 16-19 of the protocol.

Study population

The study population includes individuals aged 12 years and older in the HealthVerity COVID-19 database. More specifically, for the SCCS study design (primary and secondary objectives), the study population includes individuals aged 12 years and older who received at least one dose of a Novavax COVID-19 Vaccine and experienced an AESI following vaccination. Sample size estimates needed to evaluate the primary objective based on each AESI are listed in the protocol (See Table 3, page 49 and Appendix 4 of the protocol).

Data collection

Claims data submitted to insurance companies and aggregated by HealthVerity include de-identified person-level inpatient, outpatient, and pharmacy claims data from April 1, 2020 – April 30, 2025. AESIs will be identified using ICD-10-CM diagnosis codes. See Table 1, pages 42-43 of protocol version 5.0 for a list of AESIs, including clean and risk windows.

Data analysis

The primary objective will be assessed using conditional Poisson regression models to compare incidence rates during risk windows to incidence rates during control windows for each AESI overall, by dose number, and by subgroup. Exploratory objectives will be assessed using a Cox proportional hazards model for matched pairs to determine hazard ratios for each AESI between Novavax COVID-19 vaccine recipients and referent groups (recipients of Pfizer COVID-19 vaccine, recipients of Moderna COVID-19 vaccine, and unvaccinated individuals, respectively).

Milestone dates

Milestone dates listed in the updated PVP (Version 3.6) are as follows:

- Interim Report Submission: September 30, 2025; September 30, 2026; September 30, 2027
- Study Completion Date: September 30, 2027
- Final Report Submission: September 30, 2028

Interim results

According to the most recently submitted Interim Report (Interim Report #2, submitted to IND 22430/0.685, data cutoff date September 20, 2023), a total of 3,996 individuals aged 12 years and older had received at least one dose of the Novavax COVID-19 vaccine and were eligible for inclusion in the analysis. Among these participants, 249 (6.2%) experienced an incident AESI in the post-vaccination risk or control periods. Due to the limited sample sizes, comparative analyses were not performed. Descriptive analyses reported baseline characteristics and AESIs counts. However, no safety conclusions were drawn based on the limited data so far.

7.2.3 Study 2019nCoV-405: Global Safety Surveillance Study of Pregnancy and Infant Outcomes Study Using C-VIPER

Note: For a detailed review of the study protocol for Study 2019nCoV-405, see the following review memos (b) (6)

- *Pregnancy Registry Protocol Review Memorandum dated July 13, 2022 (Review of protocol version 2.0, dated March 7, 2022, submitted to IND 22430/0.258 on March 30, 2022)*
- *Pregnancy Registry Amended Protocol Review Memorandum dated January 25, 2024 (Review of protocol version 3.0, dated August 23, 2023, submitted to IND 22430/0.559 on November 7, 2023)*

Study title
Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

Study design
C-VIPER is an international, non-interventional, postmarketing/post-authorization, prospective cohort study among women vaccinated with a COVID-19 vaccine during pregnancy or within 30 days prior to the first day of the last menstrual period (LMP). C-VIPER is a multiproduct pregnancy registry used to study multiple COVID-19 vaccines, including Novavax COVID-19 Vaccine, Adjuvanted.

Study objectives
The objective of C-VIPER as stated in the protocol is “to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID-19 vaccine” (page 1, protocol v3.0). This includes evaluation of both primary and booster vaccinations (homologous or heterologous).

Study population
The study population includes two cohorts of pregnant women aged 18 years of age and older, matched by country and gestational age (+/- 2 weeks):

- Cohort 1 (Novavax cohort): Pregnant women exposed to at least one dose of Novavax COVID-19 Vaccine from 30 days prior to the first day of the LMP to end of pregnancy. These participants are enrolled as part of the C-VIPER.
- Cohort 2 (Reference cohort): Pregnant women unexposed to a COVID-19 vaccine from 30 days prior to the first day of the LMP to end of pregnancy. These

participants are enrolled through the Pregistry International Exposure Registry (PIPER).

The planned sample size is a minimum of 500 pregnancies in Cohort 1 and a minimum of 1000 pregnancies for Cohort 2.

Data collection
Participants are asked to complete various structured web-based questionnaires or modules, which collect self-reported information. Participants are also asked to submit de-identified medical records. In addition, the study team may assist in retrieval of medical records where local law permits. De-identified medical records are used to adjudicate self-reported diagnoses. Data collection occurs from the time of maternal enrollment through a follow-up time when infants are 12 months of age. Total study duration is planned for 5 years. Outcomes to be assessed are listed in Table 1, page 31-32 of study protocol v3.0 (IND 22430/0.559).

Data analysis
The main data analysis includes a comparison of baseline characteristics of the two cohorts as well as both unadjusted and adjusted analyses comparing the frequency of outcomes of interest between the two cohorts. Methods of confounder adjustment include propensity score (PS)-stratification, inverse probability of treatment weighting (IPTW), and matching.

Milestone dates
Milestone dates listed in the updated PVP (Version 3.6) are as follows:

- Interim Report Submissions: June 30, 2025; June 30, 2026
- Study Completion Date: February 28, 2027
- Final Report Submission: June 30, 2027

Interim results
According to the most recently submitted Progress Report (Progress Report #2, submitted to IND 22430/0.651, covering reporting period September 1, 2023 – April 30, 2024), among the 16 participants analyzed to date, 31 adverse events have been reported, and no safety signals have been identified.

Reviewer comment: Each of the ongoing safety-related post-authorization studies includes both the original strain of the Novavax vaccine (NVX-CoV2373; prototype Wuhan strain) as well as the updated formulations for 2023-2024 (NVX-CoV2601; XBB.1.5 strain) and 2024-2025 (NVX-CoV2705; JN.1 strain). No safety signals have been identified to date in these studies, although there has been limited uptake and insufficient data to draw meaningful conclusions.

On November 6, 2024, (b) (6) *convened a Vaccine Safety Team (VST) meeting to discuss the proposed postmarketing safety studies for this original BLA. For context, we compared the proposed Novavax studies to PMRs for currently approved mRNA COVID-19 Vaccines (Comirnaty [BLA 125742] and Spikevax [BLA 125752]). Lastly, we considered the implications of findings from the recently published MACiV*

study, which showed persistent late gadolinium enhancement in patients aged ≤30 years of age with a clinical diagnosis of acute myocarditis after COVID-19 vaccination [16].

At this meeting there was preliminary agreement that ongoing post-authorization safety studies (Studies 2019nCoV-402 and 2019nCoV-404) would be PMRs, and the ongoing post-authorization pregnancy registry (Study 2019nCoV-405) would be a PMC. In addition, attendees agreed that there was a need for a postmarketing study to evaluate for potential long-term sequelae of myocarditis after Novavax vaccination, similar to PMRs for the currently approved mRNA COVID-19 vaccines.[8] Lastly, attendees considered whether a subclinical myocarditis study might be necessary (similar to PMRs for the currently approved mRNA COVID-19 vaccines), but decided against this for the following reasons:

- *There is no validated biomarker for subclinical myocarditis.*
- *From experience with mRNA COVID-19 vaccine studies, there are challenges with the interpretation of data on cardiac troponin levels to evaluate for subclinical myocarditis.*
- *When assessing cardiac troponin levels in asymptomatic individuals, there is increasing likelihood of confounding with increasing age due to underlying cardiovascular disease or risk factors.*
- *No new safety signals have emerged from the completed/ongoing studies evaluating troponin levels following administration of mRNA COVID-19 vaccines.*

On December 5, 2024, the Sponsor responded to our information request sent on November 13, 2024 (CBER IR #31). In their response (BLA 125817/0.49), the Sponsor included a protocol synopsis for a study to evaluate long-term sequalae of myocarditis following vaccination as well as an updated PVP (Version 3.3). This protocol synopsis is reviewed in Section 7.2.4.

On December 10, 2024, the Novavax BLA review team met to discuss PMR/PMC studies for the Novavax original BLA. The review team concurred with recommendations from the VST meeting.

On January 23, 2025, this reviewer presented the proposed PMR/PMC study designations for the proposed postmarketing safety studies to the CBER Safety Working Group (SWG). SWG members concurred with the following PMR/PMC designations:

- *Study 2019nCoV-402 -> PMR*

[8] Although myocarditis and pericarditis are included as pre-specified outcomes in Studies 2019nCoV-402 and 2019nCoV-404, these studies were not designed to evaluate long-term outcomes of myocarditis after vaccination, and there has been limited vaccine uptake and no myocarditis cases to date (as of December 5, 2024). In addition, (b) (6) performed an Active Postmarket Risk Identification and Analysis (ARIA) assessment and determined that the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA (the Sentinel program) is not sufficient to evaluate this serious risk. Data sources in the CBER Surveillance Program (CSP) are not sufficient to identify the outcomes due to uncertainties with vaccine uptake. Although uncertainties about vaccine uptake could affect any postmarketing study of Novavax vaccine, the Sponsor may have access to additional data sources.

- *Study 2019nCoV-404 -> PMR*
- *Study 2019nCoV-405 -> PMC*
- *Long-term sequalae of myocarditis study -> PMR*

On January 29, 2025, due to low vaccine uptake in ongoing studies 2019nCoV-404 and 2019nCoV-402, (b) (6) *sent an IR to the Sponsor recommending that they consider extending the milestone dates for study completion and final study report submission by 2 years or more (CBER IR #47). On February 3, 2024, the Sponsor responded and agreed to extend the milestone dates for Studies 2019nCoV-402 and 2019nCoV-404 by two years to allow for adequate vaccine uptake.*

7.2.4 Study 2019nCoV-418: Long-term sequelae of myocarditis and pericarditis study

In response to our information request sent on November 13, 2024, the Sponsor submitted a synopsis of a post-authorization safety study (PASS) to evaluate long-term sequalae of myocarditis following vaccination (BLA 125817/0.49). Subsequently, an updated synopsis (appended to PVP Version 3.6) was submitted to BLA 125817/0.102.

Study title
Post-Authorization Safety Study to Evaluate Potential Long-Term Sequalae of Myocarditis and Pericarditis Following Vaccination

Study design
This study is an observational, retrospective cohort study conducted using a US-based, EHR-linked claims database.

Study objectives
The primary objective is “to evaluate the clinical course and potential long-term cardiac sequelae among individuals diagnosed with myocarditis and/or pericarditis following receipt of at least one dose of a Novavax COVID-19 vaccine.”

Study population
The study population will include individuals aged 12 years and older in the claims database who experienced post-vaccination myocarditis and/or pericarditis within 30 days of receipt of a Novavax COVID-19 vaccine dose. (See page 27 of PVP Version 3.6 for additional details on inclusion/exclusion criteria.)

Data collection
Individuals will be identified within a large US-based, EHR-linked claims database. Potential data sources include Optum, Veradigm, and Carelon. The Sponsor will conduct a feasibility assessment prior to selecting a database. Individuals identified with claims for incident myocarditis and/or pericarditis after Novavax vaccination will be followed for up to 5 years after the index date. Cases will be identified using claims data and subsequently evaluated in detail using the linked EHR data.

Data analysis

This study is descriptive only and there is no referent group. Likewise, an *a priori* sample size has not been determined. Descriptive statistics will include mean, standard deviation, median, interquartile range (for continuous variables), and counts and percentages (for categorical variables). Further details will be provided in a statistical analysis plan. A range of study outcomes will be described for individuals in the study, including myocarditis- and pericarditis-related treatments and procedures as well as long-term cardiac outcomes such as heart failure, arrhythmia, recurrent myocarditis, late gadolinium enhancement, hospitalization, and death. (See Table 1, page 28-29 of PVP Version 3.6, for a full list of planned outcomes.) Lastly, covariates will be analyzed to determine risk factors.

Milestone dates

Milestone dates listed in the updated PVP (Version 3.6) are as follows:

- Final protocol submission: January 31, 2026
- Study Completion Date: December 31, 2031
- Final report submission: September 30, 2032

Reviewer comment: As we have seen with the current post-authorization studies to date, a significant limitation for Novavax post-authorization studies has been the low uptake of the Novavax COVID-19 vaccine in the US. In addition, the rare incidence of post-vaccination myocarditis and the limited US population coverage of claims databases with EHR-linkage pose additional challenges for capturing postmarketing cases for study. Therefore, this reviewer agrees with the Sponsor's plan to perform a feasibility study prior to performing a retrospective cohort study using EHR-linked claims data. Strengths of this approach include the ability to identify rare outcomes retrospectively and follow them longitudinally, the ability to confirm cases with details from the medical record, and the ability to assess for possible risk factors among incident cases. Additional limitations include potential confounding by prior mRNA COVID-19 vaccination and typical limitations of claims/EHR data (e.g., missing or incomplete information, misclassification, lack of information on health behaviors or demographics, etc.). Finally, this proposed study is generally comparable to similar PMRs for Comirnaty (PMR #7) and Spikevax (PMR #6), both of which are also descriptive in nature. On January 27, 2025, FDA provided feedback on the proposed study synopsis (CBER IR #46), including a recommendation to include pericarditis cases. On February 3, 2024, the Sponsor responded and agreed to include pericarditis in the proposed study. They also provided the updated study number and title: Study 2019nCoV-418, "Post-Authorization Safety Study to Evaluate Long-Term Sequalae of Myocarditis and Pericarditis Following Vaccination." Lastly, the Sponsor updated their study synopsis to include pericarditis in their updated PVP (Version 3.4, dated February 6, 2025) submitted on February 11, 2025 (BLA 125817/0.69) as well as the updated PVP (Version 3.6, dated March 25, 2025) submitted on March 26, 2025 (BLA 125817/0.102).

8 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

8.1 Important Identified Risks

8.1.1 Anaphylaxis

Anaphylaxis is an acute, potentially life-threatening allergic reaction characterized by rapid onset of symptoms typically affecting more than one body system (i.e., skin/mucosal, respiratory, cardiovascular [hypotension], and/or gastrointestinal symptoms) [17]. Allergic reactions, including anaphylaxis, can occur following any vaccine and can be due to the vaccine antigen itself or some other vaccine component [18]. During the COVID-19 pandemic, anaphylaxis was identified soon after rollout of the mRNA COVID-19 vaccines in the US as a serious risk associated with COVID-19 vaccination [19]. CDC has published recommendations for the management of anaphylaxis after COVID-19 vaccination, which provide additional details on prevention, recognition, and management of anaphylaxis [20].

Although there were no reported SAEs of anaphylactic reaction attributed to Novavax vaccine in the Integrated Summary of Safety (page 742), postmarketing data (described in Section 6.1 and 6.2) support the categorization of anaphylaxis as an Important Identified Risk.

Sponsor-proposed mitigation strategies for anaphylaxis include routine pharmacovigilance, targeted AE follow-up questionnaire, and inclusion of this AE in the ongoing clinical trial (2019nCoV-301) and post-authorization safety studies (2019nCoV-404, 2019nCoV-402). In addition, the proposed USPI describes "anaphylaxis" (Contraindications, Postmarketing Experience), "acute allergic reactions" (Warnings and Precautions), and "hypersensitivity reactions" (Clinical Trials Experience).

Reviewer comment: The Sponsor's proposed mitigation strategies for anaphylaxis are acceptable.

8.1.2 Myocarditis and/or pericarditis

Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the pericardium) can be caused by a broad range of infectious (viral, bacterial, fungal, and parasitic) and non-infectious causes (autoimmune/inflammatory, oncologic, metabolic, and vaccine-associated). Historically, vaccine-associated myocarditis has been reported following vaccination of military recruits with smallpox vaccination [21]. During the COVID-19 pandemic, after rollout of the mRNA COVID-19 vaccines in the US, myocarditis and pericarditis were identified as adverse events that occurred more frequently than expected following mRNA COVID-19 vaccination [22]. Multiple lines of evidence later confirmed a causal relationship between mRNA COVID-19 vaccination and myocarditis and pericarditis, with the greatest risk among adolescent and young males within 7 days of the second dose of an mRNA COVID-19 vaccine [23]. In response to this safety signal, FDA updated EUA Fact Sheets to communicate this risk and mandate reporting of post-authorization cases and the CDC published guidance to aid healthcare providers in the identification and management of this risk [22].

At the time of initial EUA for the Novavax COVID-19 Vaccine, Adjuvanted, the Sponsor agreed to FDA's request to list myocarditis and/or pericarditis as an Important Identified Risk in the PVP. In addition to the evidence from mRNA COVID-19 vaccines, this decision was supported by reports of myocarditis and pericarditis following Novavax COVID-19 vaccination in both the clinical trial setting and foreign postmarketing setting. (See Pharmacovigilance EUA Memorandum dated July 13, 2022, (b) (6) for more details). Since then, ongoing evaluation of postmarketing data (described in Section 6.1 and 6.2) has supported the categorization of myocarditis and/or pericarditis as an Important Identified Risk.

Sponsor-proposed mitigation strategies for myocarditis and/or pericarditis include routine pharmacovigilance, targeted AE follow-up questionnaire, expedited reporting of postmarketing cases to VAERS, and inclusion of this AE in the ongoing clinical trial (2019nCoV-301) and post-authorization safety studies (2019nCoV-404, 2019nCoV-402) as well as the planned long-term sequelae of myocarditis and pericarditis study (2019nCoV-418). In addition, the proposed USPI describes myocarditis and/or pericarditis (Warnings and Precautions, Clinical Trial Experience, and Postmarketing Experience).

Reviewer comment: The Sponsor's proposed mitigation strategies for myocarditis and/or pericarditis are acceptable.

8.2 Important Potential Risks

8.2.1 Atrial fibrillation and/or atrial flutter

Atrial fibrillation is the most commonly treated cardiac arrhythmia [24]. Men and women aged 40 years and older have a 1 in 4 lifetime risk of developing atrial fibrillation [25]. Risk factors for atrial fibrillation include advancing age, hypertension, obesity, European ancestry, heart failure, ischemic heart disease, hyperthyroidism, chronic kidney disease, moderate to heavy alcohol use, smoking, and left atrial enlargement [24]. A recent study estimated the prevalence of atrial fibrillation in the US to be 10.55 million (4.5% of the US adult population) [26]. Another recent US study demonstrated an age and sex standardized incidence of 6.82 (95% CI, 6.65-7.00) cases per 1000 person-years [27]. The incidence of atrial fibrillation increases with age, with adults aged 65 years and older having an incidence of 19.2 per 1000 person-years [28]. Although atrial flutter is thought to be less common than atrial fibrillation, the two entities are clinically related and often coexist [29, 30].

Atrial fibrillation emerged during the review as a late-breaking issue based on the clinical reviewer's analysis of clinical trial cases. See the clinical reviewer's memo for additional details of their analysis and section 11 "Late-breaking issues addendum" of this memo for this reviewer's analysis of relevant VAERS reports.

Sponsor-proposed mitigation strategies for atrial fibrillation and/or atrial flutter include routine pharmacovigilance, expedited reporting of postmarketing cases to VAERS, and inclusion of atrial fibrillation and atrial flutter in post-authorization safety studies (2019nCoV-404, 2019nCoV-402).

Reviewer comment: The Sponsor's proposed mitigation strategies for atrial fibrillation and/or atrial flutter are acceptable.

8.2.2 Cerebrovascular accident

Cerebrovascular accident, or stroke, refers to brain damage that results from either blockage of blood supply to the brain (ischemic stroke) or rupture of a blood vessel in the brain (hemorrhagic stroke) [31]. Cerebrovascular accident is one of the leading causes of death in the United States [32]. Risk factors for cerebrovascular accident, which are common in the US adult population, include high blood pressure, high cholesterol, smoking, obesity, and diabetes. In 2019, there were 0.46 (0.4-0.52) million incident cases in the US, with a prevalence of 7.09 (6.41-7.85) million cases [33].

Cerebrovascular accident emerged during the review as a late-breaking issue based on the clinical reviewer's analysis of clinical trial cases. See the clinical reviewer's memo for additional details of their analysis and section 11 "Late-breaking issues addendum" of this memo for this reviewer's analysis of relevant VAERS reports.

Sponsor-proposed mitigation strategies for cerebrovascular accident include routine pharmacovigilance, expedited reporting of postmarketing cases to VAERS, and inclusion of this AE in ongoing post-authorization safety studies 2019nCoV-404, 2019nCoV-402 (already included as "hemorrhagic stroke" and "non-hemorrhagic stroke").

Reviewer comment: The Sponsor's proposed mitigation strategies for cerebrovascular accident are acceptable.

8.2.3 Cranial nerve VIII disorders (including vestibular neuronitis)

Vestibular neuronitis is a condition characterized by vertigo, nausea, and imbalance, and is caused by inflammation of the eighth cranial nerve. Vestibular neuronitis is often associated with a preceding viral infection and the clinical course is benign and self-limited [34]. Estimates of the incidence of vestibular neuronitis range from 3.5 to 48.5 per 100,000 person-years [35-37].

Cranial nerve VIII disorders (including vestibular neuronitis) emerged during the review as a late-breaking issue based on the clinical reviewer's analysis of a clinical trial case. See the clinical reviewer's memo for additional details of their analysis and section 11 "Late-breaking issues addendum" of this memo for this reviewer's analysis of relevant VAERS reports.

Sponsor-proposed mitigation strategies for cranial nerve VIII disorders (including vestibular neuronitis) include routine pharmacovigilance, expedited reporting of postmarketing cases to VAERS, and inclusion of cranial nerve VIII disorders (including vestibular neuronitis) in post-authorization safety studies (2019nCoV-404, 2019nCoV-402).

Reviewer comment: The Sponsor's proposed mitigation strategies for cranial nerve VIII disorders (including vestibular neuronitis) are acceptable.

8.2.4 Ocular motor cranial nerve disorders

Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI) are caused by a range of etiologies: congenital, traumatic, microvascular, neoplastic, and idiopathic [38, 39]. Although considered rare in general, ocular motor cranial nerve disorders are among the most common of cranial nerve disorders [40, 41]. In addition, people living with diabetes, those with ischemic risk factors, and older adults are at increased risk [41-43].

Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI) has been an Important Potential Risk in the Novavax COVID-19 Vaccine, Adjuvanted PVP since the authorization of the 2023-2024 Formula. During the review for 2023-2024 Formula EUA amendment, two clinical trial cases from Study 2019nCoV-311 reported AEs of trochlear nerve (4th cranial nerve) palsy and abducens nerve (6th cranial nerve) palsy. Both cases reported a close temporal relationship to vaccination. However, both cases also reported multiple confounding risk factors (such as history of diabetes, other microvascular risk factors, and/or prior cranial nerve disorders), and both cases occurred in a clinical trial study period without a placebo control group. Therefore, FDA asked the Sponsor to add ocular motor cranial nerve disorders as an Important Potential Risk in the PVP, expedite reporting of any postmarketing cases, periodically review postmarketing cases, and include ocular motor nerve disorders as an AESI in the ongoing post-authorization safety studies. (See Pharmacovigilance EUA Amendment Memorandum dated October 3, 2023, (b) (6) for more details).

During the 2023-2024 season, VAERS received a single postmarketing case of a 3rd cranial nerve palsy in a 72-year-old woman (VAERS ID #2704572). Like the premarket clinical trial cases, this case demonstrated a temporal relationship to vaccination, but also was confounded by risk factors for ocular motor cranial nerve palsy (age, diabetes mellitus, and hypertension) and lacked a placebo control. This case was discussed at a Vaccine Safety Team (VST) meeting on November 16, 2023, and the group concurred with continued monitoring for this AE. As noted in section 6.2.1 VAERS Reports, no additional unique cases have been identified since then.

Sponsor-proposed mitigation strategies for ocular motor cranial nerve disorders include routine pharmacovigilance, expedited reporting of postmarketing cases to VAERS, and inclusion of this AE in the ongoing clinical trial (2019nCoV-301) and post-authorization safety studies (2019nCoV-404, 2019nCoV-402).

Reviewer comment: Although there remains insufficient evidence to support a causal relationship to vaccination, there has been limited uptake of vaccine since these clinical trial cases were identified. Therefore, it is reasonable to keep "Ocular motor cranial nerve disorders" as an Important Potential Risk. The Sponsor's proposed mitigation strategies for ocular motor cranial nerve disorders are acceptable.

8.3 Important Missing Information

The following safety concerns are listed as Missing Information in the PVP (Version 3.6) submitted in support of this BLA:

- Use in pregnancy and while breastfeeding
- Use in immunocompromised patients
- Use in frail patients with comorbidities
- Use in patients with autoimmune or inflammatory disorders
- Interaction with other vaccines
- Long-term safety

Each of these safety concerns was included in the PVP for the original EUA based on a lack of clinical trial data due to exclusion criteria (pregnancy and breastfeeding, immunocompromised, frail patients with comorbidities, patients with autoimmune/inflammatory disorders), likelihood of co-administration (interaction with other vaccines), and need for longer-term safety data. (See Pharmacovigilance EUA Memorandum dated July 13, 2022, (b) (6) for additional details).

Reviewer comment: Since the initial US authorization, additional safety data have accrued from both clinical trials and postmarketing experience. However, given the limited uptake of the vaccine in the US, continued inclusion of each of these safety concerns as Missing Information is warranted.

9 (b) (6) ASSESSMENT

Review of available data is largely consistent with the known safety profile for Novavax COVID-19 Vaccine, Adjuvanted. No new safety signals emerged from review of safety data reviewed in the ISS or from postmarketing experience.

"Myocarditis and pericarditis" are known serious risks and warrant further characterization via FDAAA Title IX PMR safety studies: two existing post-authorization studies (Study 2019nCoV-402, Study 2019nCoV-404) and a planned study to evaluate long-term sequelae of myocarditis and pericarditis following vaccination (2019nCoV-418). The review team's safety study PMR recommendations were presented to the CBER Safety Working Group (SWG) on January 23, 2025, and SWG concurred with this regulatory approach.

The clinical team noted small numerical imbalances (vaccine vs. placebo) in clinical trial cases of atrial fibrillation and cerebrovascular accident (CVA) (please see clinical review memorandum and final labeling language in 6.1 Clinical Trials Experience section of USPI). The clinical team's review of the atrial fibrillation and CVA cases indicated that risk factors and predisposing medical conditions were present in some cases, there was no clear pattern in time of onset to suggest specific pathophysiologic mechanism for causal relationship to vaccination, and biological plausibility was uncertain. Atrial fibrillation is known to increase with age and has a high background rate (an estimated 4.5% of the US adult population has atrial fibrillation [26]). In response to a CBER IR

#62, the applicant confirmed that no safety signals were identified for atrial fibrillation and CVA from postmarketing data. Given the uncertain biological plausibility for atrial fibrillation and CVA, the review team recommended postmarketing commitment (PMC) safety studies for atrial fibrillation and CVA, and presented these recommendations to the SWG on March 13, 2025. The SWG concurred with this approach and a PMC notification was issued to the applicant on March 17, 2025.

The clinical team also noted small numerical imbalances in cardiac failure and cardiomyopathy and a decision was made by the review team to require expedited reporting (15-day reports to VAERS regardless of seriousness or expectedness) for these events for 3 years following licensure.

The ongoing pregnancy registry (Study 2019nCoV-405) will continue as a PMC. In addition, the safety of NUVAXOVID can be monitored through routine PV activities and risk communication through labeling.

The Sponsor's proposed PVP (Version 3.6, dated March 25, 2025) is acceptable.

10 (b) (6) RECOMMENDATIONS

Should this product be approved, (b) (6) has the following recommendations for postmarketing safety monitoring of NUVAXOVID:

- Routine pharmacovigilance in accordance with adverse event reporting regulations under 21 CFR 600.80 and described in the Sponsor's proposed PVP.
- Enhanced pharmacovigilance with expedited (15-day) reporting to VAERS for the following events, regardless of seriousness or expectedness, for 3 years following initial approval: myocarditis and/or pericarditis; atrial fibrillation and/or atrial flutter; cerebrovascular accident; ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI); cranial nerve VIII disorders (including vestibular neuronitis; cardiac failure; and cardiomyopathy.

<u>Postmarketing Requirements under Section 505(o) of FDCA to assess serious risks of myocarditis and pericarditis</u>

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

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

- 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

- 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

<u>Postmarketing Commitments subject to reporting requirements under Section 506B</u>

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

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

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

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

- 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

At this time, the available safety data do not suggest a safety concern that would require a REMS. Please see the final version of the package insert submitted by the Sponsor for the final agreed-upon language for the label.

11 LATE-BREAKING ISSUES ADDENDUM

3/19/25: This addendum describes several late-breaking issues that were analyzed by the review team after the main text for this memo was written. During labeling discussions, the clinical review team identified clinical trial imbalances in certain internal analyses of cases of atrial fibrillation and cerebrovascular accident for study 2019nCoV-301 as well as a clinical trial case of vestibular neuronitis that was concerning for possible relation to vaccination. This led to broader review team discussions, additional communications with the Sponsor, additional analyses, and ultimately a change in the pharmacovigilance plan.

After the clinical review team identified these issues, the review team asked the Sponsor to provide additional analyses to provide context for further discussion. On March 7, 2025, FDA sent CBER IR #62 to the Sponsor requesting additional analyses regarding supraventricular tachyarrhythmias (especially atrial fibrillation/flutter), cerebrovascular accident, and inner ear / cranial nerve VIII disorders (including tinnitus, vertigo, and vestibular neuronitis). In addition, FDA asked the Sponsor whether atrial fibrillation, atrial flutter, and cranial nerve VIII disorders (including vestibular neuronitis) could be added to the two ongoing active surveillance postmarketing safety studies (Study 2019nCoV-404 and Study 2019nCoV-402).

On March 10, 2025, the Sponsor responded, providing the requested analyses, and confirming that they could add the requested safety outcomes to their ongoing postmarketing safety studies. The Sponsor also concluded that there was no clear evidence of a causal association between the Novavax COVID-19 vaccine and outcomes of supraventricular tachyarrhythmias or cerebrovascular accident based on the lack of significant risk differences observed in their clinical trial data and lack of safety signals identified in postmarketing data. For additional details on the Sponsor's analysis see their response submitted to BLA 125817/0.87.

On March 13, 2025, the review team discussed these issues further at a Safety Working Group (SWG) meeting. The review team proposed that FDA propose new postmarketing commitments (PMCs) for both atrial fibrillation and cerebrovascular accident (in addition to the previously discussed PMR/PMCs for myocarditis/pericarditis), with these safety issues being included in ongoing studies 2019nCoV-402 and 2019nCoV-404. The SWG concurred with these recommendations. On March 17, 2025, FDA sent the Sponsor an IR communicating these additional PMCs as well as additional pharmacovigilance activities, including:

- Addition of AEs to studies 2019nCoV-402 and 2019nCoV-404: atrial fibrillation and/or atrial flutter; cranial nerve VIII disorders (including vestibular neuronitis)

- Expedited reporting for specific AEs: myocarditis and/or pericarditis; atrial fibrillation and/or atrial flutter; cerebrovascular accident; ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI); and cranial nerve VIII disorders (including vestibular neuronitis)
- Amending the Pharmacovigilance Plan to include Important Potential Risks: atrial fibrillation and/or atrial flutter; cerebrovascular accident; and cranial nerve VIII disorders (including vestibular neuronitis)

On March 18, 2025, the Sponsor responded (BLA 125817/0.96), confirming the additional PMCs. On March 19, 2025, the Sponsor submitted an updated PVP (Version 3.5, BLA 125817/0.98). On March 26, 2025, the Sponsor submitted an updated PVP (Version 3.6, BLA 125817/0.102).

The below VAERS analyses were performed during review of these late-breaking issues. None of the VAERS analyses were supportive or suggestive of a new safety signal.

Vestibular neuronitis

During the labeling discussion stage of the review, the clinical review team identified a clinical trial case of concern in study 2019nCoV-311 Part 2. In this study, a 41-year-old female subject (b) (6)) experienced an AESI of vestibular neuronitis which occurred both 11 days after the first booster vaccination with NVX-CoV2373 and again 16 days after the second booster dose with NVX-CoV2373. Both the investigator and the Sponsor considered this case related to NVX-CoV2373 based on the positive re-challenge following the second vaccination.

In response to this case, this reviewer queried the VAERS database on March 7, 2025, for all VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted under the HLGT “Inner ear and VIIIth cranial nerve disorders” (including secondary PTs). This query returned 41 reports. Findings are summarized below:

Of the 41 reports, 28 were from the US and 13 were foreign reports. Twenty reports were non-serious and non-otherwise medically important conditions (OMIC), 13 reports were OMIC, and 8 reports were serious. There were no deaths. Review of Preferred Terms (PTs) showed that 23 reports were for tinnitus, 15 reports were for vertigo, 2 reports were for tinnitus and vertigo, and 1 report was for vestibular neuronitis. (Many reports also reported other symptoms, but these are the predominant inner ear- and/or cranial nerve VIII-related symptoms reported). For reports with reported age, the median age was 43 years (range 18-78 years). For reports with reported sex, there were 28 females and 12 males. For reports with reported time to onset, the median time to onset was 2 days (range 0-466 days). Many of the reported cases had limited information and only 2 reports included medical records. The case of vestibular neuronitis was a foreign report with limited clinical information that described the onset of dizziness, vestibular neuronitis, lymphoid tissue hyperplasia, and pubic abscess in a 32-year-old female with onset 7 days after vaccination.

Reviewer comment: Review of VAERS reports under the HLGT "Inner ear and VIIIth cranial nerve disorders" was not suggestive of a safety signal.

Atrial fibrillation/flutter

During the labeling discussion stage of the review, the clinical review team identified atrial fibrillation/flutter and stroke as potential safety issues based on their analyses of clinical trial datasets submitted by the Sponsor.

In response to this concern, this reviewer queried the VAERS database on March 10, 2025, for all VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted under the broad SMQ "Supraventricular tachyarrhythmias." This query returned 16 reports. Findings are summarized below:

Of the 16 reports, two reported extrasystoles and/or tachycardia and were not related to atrial fibrillation or atrial flutter. Of the 14 remaining reports, 9 were from the US and 5 were foreign reports. Seven reports were serious, 6 were OMIC, and 1 was non-serious and non-OMIC. There were no deaths. Review of PTs showed that 13 reports were for atrial fibrillation and 1 report was for atrial fibrillation, atrial flutter, and ventricular tachycardia. Of these 14 reports for atrial fibrillation and/or atrial flutter, 3 reports describe a history of atrial fibrillation or atrial flutter preceding vaccination, and 3 reports had other confounding factors (concurrent COVID pneumonia, fluid retention in the setting of Celebrex use, and binge drinking, respectively). One report of atrial fibrillation (a foreign report with very limited information) also reported a concurrent cerebrovascular accident. For reports with reported age, the median age was 66 years (range 38-80 years). For reports with reported sex, there were 5 female and 9 males. For reports with reported time to onset, the median time to onset was 8.5 days (range 0-388 days). (Note: A total of 10 cases had reported onset within 30 days of vaccination). Many reports contained limited clinical information and 6 reports included medical records.

Reviewer comment: Review of VAERS reports under the broad SMQ "Supraventricular tachyarrhythmias" was not suggestive of a safety signal.

Cerebrovascular accident

In addition, this reviewer queried the VAERS database on March 10, 2025, for all VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted under the HLT "Central nervous system haemorrhages and cerebrovascular accidents." This query returned 13 reports. Findings are summarized below:

Of the 13 reports, 1 was from the US and 12 were foreign reports. Most reports were serious (n=10), including 2 fatalities, and 3 were OMIC. Review of PTs showed that all reports were for cerebrovascular accident and one report also included a PT for atrial fibrillation. For reports with reported age, the median age was 75 years (range 20-96

years). For reports with reported sex, there were 6 females and 6 males. For reports with reported time to onset, the median time to onset was 11 days (range 0-67 days). Many reported cases had limited information and only 1 report included medical records. Review of death reports revealed multiple confounding factors.

Reviewer comment: Review of VAERS reports under the HLT "Central nervous system haemorrhages and cerebrovascular accidents" was not suggestive of a safety signal.

Bell's palsy

In response to a request by the clinical review team, this reviewer queried the VAERS database on March 7, 2025, for all VAERS reports for Novavax COVID-19 Vaccine, Adjuvanted with the PTs "Bell's palsy" and/or "Facial paralysis." This query returned 17 reports. Findings are summarized below:

Of the 17 reports, one was a duplicate report and two reports described symptoms concerning for other diagnoses (GBS and TIA, respectively). Of the 14 remaining cases, 2 were from the US and 12 were foreign reports. Considering all reports (US and foreign), 8 cases were female and 6 were male. The median age was 47 years (range 20-77 years) and the median time to onset was 9 days (range 0-73 days). There were no deaths, and most cases were serious (n=3) or OMIC (n=10). None of the cases included medical records. Many of the foreign reports contained limited clinical information other than the reported AE of facial paralysis. The first US report (OMIC) describes a case of Bell's palsy in a 34-year-old pregnant woman that occurred 73 days after vaccination. The prolonged time since vaccination and the risk factors of obesity and pregnancy make this case less likely related to vaccination. The second US report (non-serious) describes a 46-year-old female with facial paralysis 23 days after vaccination. She also experienced mottled skin of her hands, paresthesia, and right eye blurred vision. There is insufficient information to adequately assess this case.

Reviewer comment: Reviewer comment: Review of VAERS reports with the PTs "Bell's palsy" and/or "Facial paralysis" was not suggestive of a safety signal.

3/25/25 update:
Per request from the clinical review team, on March 25, 2025, (b) (6) sent an IR to the Sponsor (CBER IR #77) requesting enhanced pharmacovigilance with expedited reporting for postmarketing cases of cardiac failure and cardiomyopathy. An imbalance in cases of cardiac failure or cardiomyopathy events was observed during a previous EUA review and the imbalance is already described in the currently available Fact Sheets. In addition, the EUA review team requested that the Sponsor include cardiac failure and cardiomyopathy as prespecified safety outcomes in Studies 2019nCoV-404 and 2019nCoV-402. The Sponsor agreed to this request in their IR response received June 30, 2022 (EUA 28237/0.40). Since then neither the Sponsor nor the FDA has identified cardiac failure or cardiomyopathy as a safety signal. In addition to the request to expedite reports of cases of cardiac failure and cardiomyopathy, (b) (6) also requested an updated PVP that describes AEs for which the Sponsor has agreed to expedited

reporting. On March 26, 2025, the Sponsor responded (BLA 125817/0.102) and agreed to expedited reporting of cases of cardiac failure and cardiomyopathy. In addition, the Sponsor provided an updated PVP (Version 3.6, dated March 25, 2025) that included expedited reporting for the following AEs:

- Myocarditis and/or pericarditis
- Atrial fibrillation and/or atrial flutter
- Cerebrovascular accident
- Ocular motor cranial nerve disorders (i.e., cranial nerve disorders affecting cranial nerves III, IV, or VI)
- Cranial nerve VIII disorders (including vestibular neuronitis)
- Cardiac failure
- Cardiomyopathy

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APPENDIX
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
31-Jan-2024	Sponsor	BLA 125817/0.0	Module 1.12.5 PADER Waiver
01-Apr-2024	Sponsor	BLA 125817/0.4	Module 1.16.1 US PV Plan v3.2
01-Apr-2024	Sponsor	BLA 125817/0.4	Module 2.2 Introduction
01-Apr-2024	Sponsor	BLA 125817/0.4	Module 2.7.4 Summary of Clinical Safety
01-Apr-2024	Sponsor	BLA 125817/0.4	Module 5.3.5.3 Integrated Summary of Safety
01-Apr-2024	Sponsor	BLA 125817/0.4	Module 1.11.4 Pregnancy Analysis
07-May-2024	Sponsor	BLA 125817/1.0	Module 1.11.3 Response to CBER IR dated 30-Apr-2024 Re: VAERS Reporting
23-Aug-2024	Sponsor	BLA 125817/0.32	Module 1.14.1.3 PI_US 2024-2025 Formula_12 years and older
15-Nov-2024	Sponsor	BLA 125817/0.45	Module 1.14.1.3 PI_US 2024-2025 Formula_12 years and older PFS Single Dose
26-Nov-2024	Sponsor	IND 22430/0.701	Module 5.3.6 Summary Safety Report (SSR) #32 (01-Aug-2024 to 31-Oct-2024)
05-Dec-2024	Sponsor	BLA 125817/0.49	Module 1.11.3 Response to CBER IR 31 dated 13-Nov-2024 Re: New myocarditis study
05-Dec-2024	Sponsor	BLA 125817/0.49	Module 1.11.3 Response to CBER IR 33 dated 19-Nov-2024 Re: US PVP milestone dates
05-Dec-2024	Sponsor	BLA 125817/0.49	Module 1.11.3 Protocol Synopsis, Post-Authorization Safety Study to Evaluate Long-Term Sequelae of Myocarditis Following Vaccination
05-Dec-2024	Sponsor	BLA 125817/0.49	Module 1.16.1 US PV Plan v3.3
24-Jan-2025	Sponsor	BLA 125817/0.64	Module 1.14.1.3 PI_US 2024-2025 Formula_12 years and older PFS Single Dose
3-Feb-2025	Sponsor	BLA 125817/0.68	Module 1.11.3 Response to CBER IR 46 dated 27 January 2025 re: PASS Synopsis
3-Feb-2025	Sponsor	BLA 125817/0.68	Module 1.11.3 Response to CBER IR 47 dated 29 January 2025 re: Milestones for Study 402, Study 404
11-Feb-2025	Sponsor	BLA 125817/0.69	Module 1.16.1 US PV Plan v3.4
10-Mar-2025	Sponsor	BLA 125817/0.87	Module 1.11.3 Response to CBER IR62 dated 07Mar2025 Re: Postmarketing Safety Database

Date	Source	Document Type	Document(s) Reviewed
18-Mar-2025	Sponsor	BLA 125817/0.95	Module 1.14.1.3 PI_US 2024-2025 Formula_12 years and older PFS Single Dose
18-Mar-2025	Sponsor	BLA 125817/0.96	Module 1.11.3 Response to CBER IR72 dated 17Mar2025 Re: Acknowledgement of Postmarketing Activities
19-Mar-2025	Sponsor	BLA 125817/0.98	Module 1.16.1 US PV Plan v 3.5
26-Mar-2025	Sponsor	BLA 125817/0.102	Module 1.16.1 US PV Plan v 3.6

Table A2: (b) (6) Information Requests and Sponsor Responses

IR #	IR sent	Description of IR	Sponsor response received	STN
(b) (6) IR #1	20-Feb-2024	VAERS reports inquiry	7-May-2024	BLA 125817/1.0
(b) (6) IR #2 (CBER IR #31)	13-Nov-2024	Post-marketing Study for Long-Term Outcomes After Myocarditis	5-Dec-2024	BLA 125817/0.49
(b) (6) IR #3 (CBER IR #33)	19-Nov-2024	Milestone Dates for Post Authorization Studies	5-Dec-2024	BLA 125817/0.49
(b) (6) IR #4 (CBER IR #46)	27-Jan-2025	Feedback on long-term myocarditis study synopsis	3-Feb-2025	BLA 125817/0.68
(b) (6) IR #5 (CBER IR #47)	29-Jan-2025	Recommendation to extend milestone dates for studies 2019nCoV-404 and 2019nCoV-402	3-Feb-2025; 11-Feb-2025	BLA 125817/0.68; BLA 125817/0.69
(b) (6) IR #6 (CBER IR #62)	07-Mar-2025	Request for analysis of late-breaking issues	10-Mar-2025	BLA 125817/0.87
(b) (6) IR #7 (CBER IR #72)	17-Mar-2025	Additional PMC for atrial fibrillation and CVA; additional PV activities and updated PVP	18-Mar-2025; 19-Mar-2025	BLA 125817/0.96; BLA 125817/0.98
(b) (6) IR #8 (CBER IR #77)	25-Mar-2025	Additional PV activities and updated PVP	26-Mar-2025	BLA 125817/0.102

Abbreviations: (b) (6) Information Request (IR), submission tracking number (STN)

Table A3. Most Common PTs in Novavax vaccine VAERS reports, all reports (serious and non-serious), October 18, 2024

MedDRA Preferred Term	Count (n)	Rank
Headache	123	1
Dizziness	113	2
Fatigue	99	3
Pyrexia	91	4
Chest pain	84	5
Dyspnoea	80	6
Myalgia	77	7
Nausea	77	7
Pain	68	9
Pain in extremity	59	10
Injection site pain	54	11
Chills	49	12
Paraesthesia	49	12
Arthralgia	46	14
Cough	43	15
COVID-19	39	16
Rash	39	16
Asthenia	38	18
Malaise	38	18
Palpitations	38	18
Cellulitis	37	21
Chest discomfort	37	21
Hypoaesthesia	34	23
Pruritis	32	24
Tachycardia	32	24

Table A4. Most Common PTs in Novavax vaccine VAERS reports, serious reports only, October 18, 2024

MedDRA Preferred Term	Count (n)	Rank
Headache	71	1
Chest pain	61	2

Dyspnoea	58	3
Dizziness	57	4
Fatigue	54	5
Myalgia	54	5
Pyrexia	54	5
Nausea	41	8
Cellulitis	37	9
Cough	33	10
COVID-19	33	10
Arthralgia	30	12
Chills	29	13
Asthenia	27	14
Injection site pain	25	15
Pain in extremity	25	15
Paraesthesia	24	17
Pericarditis	24	17
Pain	23	19
Palpitations	23	19
Tachycardia	23	19
Breakthrough COVID-19	22	22
Chest discomfort	22	22
Malaise	22	22
Vaccination failure	21	25

Table A5. Most Common PTs in Novavax vaccine VAERS reports, death reports only, October 18, 2024

MedDRA Preferred Term	**Deaths (Report Period)**	**Period Rank (Deaths)**
Death	20	1
Pyrexia	7	2
Dyspnoea	4	3
Asthenia	3	4
Oxygen saturation decreased	3	4
Cerebrovascular accident	2	6

Chest pain	2	6
Cough	2	6
Dementia	2	6
Malaise	2	6
Myocardial infarction	2	6
Pulmonary oedema	2	6
Sudden death	2	6
Abdominal pain upper	1	14
Acute respiratory failure	1	14
Adverse event following immunisation	1	14
Altered state of consciousness	1	14
Anxiety	1	14
Attention deficit hyperactivity disorder	1	14
Blood cholesterol increased	1	14
Blood pressure decreased	1	14
Brain death	1	14
Breath sounds abnormal	1	14
Cachexia	1	14
Cardiac arrest	1	14
Cardiomegaly	1	14
Cardio-respiratory arrest	1	14
Cardioversion	1	14
Chronic kidney disease	1	14
Chronic obstructive pulmonary disease	1	14
Concomitant disease aggravated	1	14
Condition aggravated	1	14
Coronary artery thrombosis	1	14
C-reactive protein increased	1	14
Dehydration	1	14
Exposure to SARS-COV-2	1	14
Hypercholesterolaemia	1	14
Hyperlipidaemia	1	14
Hypertension	1	14
Hypoxia	1	14
Incorrect route of product administration	1	14

Interstitial lung disease	1	14
Lethargy	1	14
Loss of consciousness	1	14
Lung opacity	1	14
Lymph node calcification	1	14
Micturition urgency	1	14
Muscle strength abnormal	1	14
Oedema peripheral	1	14
Off label use	1	14
Overdose	1	14
Pain in extremity	1	14
Pleural effusion	1	14
Pneumonia	1	14
Pneumonitis	1	14
Pulseless electrical activity	1	14
Rales	1	14
Respiratory distress	1	14
Respiratory failure	1	14
Resuscitation	1	14
Seizure	1	14
Shock haemorrhagic	1	14
Syncope	1	14
Tachypnoea	1	14
Unevaluable event	1	14
Use of accessory respiratory muscles	1	14