Nuvaxovid : Periodic safety update report assessment

20 December 2023 to 19 June 2024

This document consists of:

1. The PRAC assessment report of the Nuvaxovid periodic safety update report (PSUR) covering the period 20 December 2023 to 19 June 2024, and;

2. The Nuvaxovid PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/13173/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010972/202406

Active substance(s): SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from spodoptera frugiperda (Nuvaxovid, Nuvaxovid XBB1.5)

Period covered by the PSUR: 19/12/2023 To: 19/06/2024

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
Nuvaxovid	Novavax CZ a.s.

Status of this report and steps taken for the assessment[1]			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	19 September 2024	19 September 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	18 November 2024	11 October 2024
☐	MS/PRAC members and MAH comments	18 December 2024	18 December 2024
☐	PRAC Rapporteur's updated assessment report following comments	6 January 2025	19 December 2024
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	16 January 2025	16 January 2025

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Declarations

☒The assessor confirms that this assessment does **not** include non-public information, including commercially confidential information (e.g. information shared by other competent authorities or organisations, reference to ongoing assessments, development plans (including Scientific Advice/Protocol

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Confidential information:

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from spodoptera frugiperda (Nuvaxovid, Nuvaxovid XBB1.5).

2. Assessment conclusions and actions

This assessment report refers to the 5th periodic benefit-risk evaluation report (PBRER)/periodic safety update report (PSUR) for Nuvaxovid (NVX-CoV2373) and Nuvaxovid XBB.1.5 (NVX-CoV2601), Coronavirus disease 2019 (COVID-19) vaccine (recombinant, adjuvanted), dispersion for injection. The active substance is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda*, with the international birth date (IBD) 20 December 2021. Nuvaxovid XBB.1.5, which is Nuvaxovid updated for the SARS-CoV-2 Omicron XBB.1.5 sub-variant, has been authorised in the European Union (EU) on 31 October 2023. This PSUR covers the 6-month interval between 20 December 2023 and 19 June 2024, with the data lock point (DLP) 19 June 2024.

All SARS-CoV-2 recombinant spike (rS) nanoparticle vaccines contain purified rS protein antigens stabilised in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against COVID-19. The vaccines are indicated for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

With this PSUR, the MAH submits responses relating to section 4.1 (issues to be addressed in the next PSUR) of the assessment report for the 4th PSUR, procedure EMEA/H/C/PSUSA/00010972/202312. The MAH confirms to address issues 1-3 (aggregate presentation of subject exposure in clinical trials, where appropriate; analyses across all post-marketing reports and separately by vaccine; information on post-authorisation use in special populations) in this 5th PSUR. As regards the list of adverse events of special interest (AESIs), the MAH incorporated acute kidney injury and acute liver injury to its list of prospectively monitored AESIs under routine surveillance. It states that results will be reported in the 6th PSUR and thereafter. According to the MAH, other AESIs on the Brighton Collaboration list fall under one of three categories of ongoing, prospective surveillance with validated signals summarised in PSURs.

According to the MAH, clinical trial exposure comprises a cumulative total of 48,380 participants exposed to at least one dose of SARS-CoV-2 recombinant, adjuvanted vaccines (rS), either monovalent or bivalent, prototype or variant. A total of 5,075 participants were engaged in blinded treatment arms of studies across the MAH-sponsored SARS-CoV-2rS clinical development program. An additional 1,422 participants were exposed to the COVID-19 influenza combination vaccine in two MAH-sponsored clinical trials. Post authorisation, according to the MAH, no doses of Nuvaxovid were distributed and 5,797 doses were administered during the reporting interval. Cumulatively, 124,790,110 Nuvaxovid doses were distributed and 2,989,177 doses were administered. During the reporting interval, 9,009,590 Nuvaxovid XBB.1.5 doses were distributed and 1,048,691 doses were reported to have been administered in Canada, the EU, South Korea, Taiwan, and the United States (US). As of the DLP, administration information from other countries/regions was not yet available to the MAH. Cumulatively, 18,101,000 and 1,201,601 Nuvaxovid XBB.1.5 doses were distributed and administered, respectively.

According to the MAH, migraine and tachycardia became validated signals during the reporting interval following health authority requests from the Therapeutic Goods Administration and the US Food and Drug

Administration (FDA), respectively. The MAH evaluated and refuted both signals. Besides, the final disposition of the previously validated signal of tinnitus was updated to refuted during the reporting interval, and tinnitus was removed from the company core data sheet (CCDS) section on adverse reactions from post-marketing experience.

The signals of anaphylaxis, paraesthesia, myopericarditis, myocarditis and pericarditis had been previously confirmed and the CCDS had been updated accordingly. Validated signals previously evaluated, refuted and closed include acute coronary syndrome associated with hypersensitivity, chest pain/chest discomfort, diarrhoea, dizziness, dyspnoea, encephalitis/encephalomyelitis, menstrual disorders, oculomotor cranial nerve disorders, syncope, sensorineural hearing loss, tachycardia and other rhythm disorders.

During the reporting interval, the EU risk management plan (RMP) was updated to include the Nuvaxovid XBB.1.5 variant vaccine (RMP Version 4.3, dated 06 March 2024) and again to include the JN.1 variant vaccine (RMP version 5.1, dated 14 June 2024), without changes to the summary of the safety concerns. Myocarditis and/or pericarditis is an important identified risk; vaccine associated enhanced disease, including vaccine-associated enhanced respiratory disease, is an important potential risk. Missing information includes the use in pregnancy and while breastfeeding, the use in immunocompromised patients, the use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders), the use in patients with autoimmune or inflammatory disorders, the interaction with other vaccines, and long-term safety. During the reporting interval, the MAH did not identify relevant new information related to these safety concerns for Nuvaxovid and Nuvaxovid XBB.1.5.

All in all, the safety profile and efficacy of Nuvaxovid and Nuvaxovid XBB.1.5 remains within the expected scope. Based on the assessment of the data presented in this PSUR, the benefit-risk balance of SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda* (Nuvaxovid, Nuvaxovid XBB1.5) remains unchanged in its authorised indications.

3. Recommendations

Based on the PRAC Rapporteur review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda* (Nuvaxovid, Nuvaxovid XBB1.5) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR

4.1. Issues to be addressed in the next PSUR:

The MAH should also address the following issues in the next PSUR

- PSUR section *Worldwide marketing authorisation status*: Information on withdrawal from marketing should be included in the core report – just as extensions of the marketing authorisation or new marketing authorisations.
- PSUR sub-section *Cumulative summary tabulations of serious adverse events from clinical trials*: The MAH is kindly asked to provide a breakdown by vaccine when presenting the summary tabulations of serious adverse events from clinical trials. Events from different studies involving the same vaccine should be aggregated.

- The MAH is kindly asked to harmonise the information provided in the core report and the appendices.

5. PSUR frequency

☒Changes of PSUR frequency are proposed

The current frequency of submission should be changed from **6 months** to **1 year** at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

Annex: updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

List of abbreviations

ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AEFI	adverse event following immunisation
AESI(s)	adverse event(s) of special interest
CCDS	company core data sheet
CI	confidence interval
CIC	COVID-19 and influenza combination
COVID-19	Coronavirus disease 2019
CSR	clinical study report
DIBD	development international birth date
DLP	data lock point
EMA	European Medicines Agency
EU	European Union
EURD	European Union reference date
EVDAS	EudraVigilance Data Analysis System
FDA	Food and Drug Administration
GMT	geometric mean titre
hACE2	human angiotensin converting enzyme 2
HIV	human immunodeficiency virus
HLT	high level term
IBD	international birth date
ICSR(s)	individual case safety report(s)
KDCA	Korean Disease Control and Prevention Agency
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralising antibody
O/E	observed to expected
PAES	post-authorisation efficacy study
PASS	post authorisation safety study
PBRER	periodic benefit-risk evaluation report
PCR	polymerase chain reaction
PLWH	people living with HIV
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT(s)	preferred term(s)
r	recombinant
RR	rate ratio
RMP	risk management plan
RSI	reference safety information
S	spike protein
SAE(s)	serious adverse event(s)
SARS-CoV-2	severe acute respiratory syndrome Coronavirus 2
SARS-CoV-2 rS	severe acute respiratory syndrome Coronavirus 2, recombinant, adjuvanted
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
SOC(s)	system organ class(es)
SRR(s)	seroresponse rate(s)
SSR	summary safety report
TEAE(s)	treatment emergent adverse event(s)
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organisation

1.1. Introduction

This 5th periodic safety update report (PSUR) for Nuvaxovid and Nuvaxovid XBB.1.5 covers the 6-month interval between 20 December 2023 and 19 June 2024. The vaccine's international birth date (IBD), as well as the European Union (EU) reference date (EURD), is 20 December 2021. The marketing authorisation holder (MAH) developed five monovalent nanoparticle study vaccines (NVX-CoV2373, NVX-CoV2515, NVX-CoV2540, NVX-CoV2601 and NVX-CoV2705) containing components of original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Wuhan strain, or variants, Omicron BA.1, Omicron BA.5, Omicron XBB.1.5, or JN.1, respectively. Currently two of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373) and Nuvaxovid XBB.1.5 (NVX-CoV2601).

All SARS-CoV-2 recombinant spike (rS) nanoparticle vaccines contain purified rS protein antigens stabilised in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against Coronavirus disease 2019 (COVID-19). The vaccines are administered intramuscularly and indicated for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. In the PSUR, the trade names, Nuvaxovid and Nuvaxovid XBB.1.5, are used when referring to these vaccines in the post-authorisation setting, while the study vaccine names, NVX-CoV2373 (or prototype) and NVX-CoV2601, are used when referring to these vaccines in clinical trials.

Table 1: Overview of the vaccines Nuvaxovid and Nuvaxovid XBB.1.5 (PSUR pp. 5 and 26)

Parameters	Nuvaxovid	Nuvaxovid XBB.1.5
Vaccine code	NVX-CoV2373	NVX-CoV2601
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5
Description	Colourless to slightly yellow and clear to mildly opalescent dispersion for injection.	
Composition	One Dose (0.5 mL) contains 5 µg of recombinant SARS-CoV-2 Spike protein produced by the recombinant DNA technology using a Baculovirus protein expression system (in an insect cell line derived from Sf9 cells of the Spodoptera frugiperda species) and 50 µg of the saponin-based adjuvant Matrix-M™ which contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of Quillaja saponaria Molina extract.	
Dosage Forms	Multi-Dose vial containing either 5 or 10 doses per vial	Multi-Dose vial containing 5 doses per vial
Indication	Active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.	
Dosage	Primary vaccination series: Administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended to administer the second Dose 3 weeks after the first dose. Booster dose: Administered intramuscularly approximately 3 months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose) Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an mRNA vaccine or adenoviral vector vaccine (heterologous booster dose).	Administered intramuscularly as a single Dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine in individuals who have previously been vaccinated. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations..

The MAH does not propose changes to the product information and/or the risk management plan (RMP) as part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

According to PSUR Appendix 4 (Table 31, pp. 306-311), Nuvaxovid was first authorised in Indonesia on 31 October 2021 (Covovax). Nuvaxovid XBB.1.5 was first authorised in the United States (US; Novavax COVID-19 vaccine, adjuvanted [2023-2024 formula]) on 03 October 2023 (PSUR Appendix 4, Table 32, pp. 311-312). In the EU, Nuvaxovid and Nuvaxovid XBB.1.5 were authorised on 20 December 2021 and on 31 October 2023, respectively.

Nuvaxovid: Nuvaxovid received marketing authorisation or emergency use authorisation as a two dose primary series and as a booster for individuals 12 years and older in several countries, the EU region and by the World Health Organisation (WHO), under the trade names Nuvaxovid, Covovax, and as Novavax COVID-19 vaccine, adjuvanted, in the US. In India, Covovax is authorised as a two-dose primary series in individuals 7 years of age and older and as a booster for individuals 18 years of age and older. In Japan, Nuvaxovid is authorised as a two-dose primary series in individuals 6 years of age and older, and as a booster in individuals 12 years of age and older.

Table 2: Nuvaxovid – invented names and countries/region of authorisation (adapted from PSUR Appendix 4, Table 31, pp. 306-311). UK, United Kingdom; WHO, World Health Organisation.

Nuvaxovid	Australia, Canada, EU, Israel, Japan, New Zealand, Singapore, South Korea, Taiwan, United Arab Emirates, UK, WHO
Covovax	Bangladesh, Brazil, India, Indonesia, Philippines, South Africa, Thailand, WHO

Nuvaxovid XBB.1.5: Nuvaxovid XBB.1.5 received authorisation for emergency use or marketing authorisation for individuals 12 years and older in seven countries, the EU region and by the WHO, under the trade names Nuvaxovid XBB.1.5, Covovax COVID-19 vaccine adjuvanted (2023-2024 formula) in Brazil, Novavax COVID-19 vaccine, adjuvanted (2023-2024 formula) in the US and Novavax COVID-19 vaccine 2023-2024 formula in South Korea.

Table 3: Nuvaxovid XBB.1.5 – invented names and countries/region of authorisation (adapted from PSUR Appendix 4, Table 32, pp. 311-312). UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Covovax COVID-19 vaccine adjuvanted (2023-2024 formula)	Brazil
Nuvaxovid XBB.1.5	Canada, EU, Singapore, Taiwan, UK, WHO
Novavax COVID-19 vaccine, adjuvanted (2023-2024 formula)	US
Novavax COVID-19 vaccine 2023-2024 formula	South Korea

The MAH notes that authorisations are pending in other regions.

Rapporteur assessment comment:

During the reporting interval, Covovax received marketing authorisation in Brazil as a primary series for individuals 12 years and older (08 January 2024), and Nuvaxovid received marketing authorisation in Japan as a primary series for individuals aged 6 years and older (04 March 2024). In Switzerland, the approval of Nuvaxovid was withdrawn (21 March 2024). Since the emergency authorisation of the updated vaccine, the prototype vaccine is no longer authorised in the US (03 October 2023).

Covovax COVID-19 vaccine adjuvanted (2023-2024 formula) received approval in Brazil, and Nuvaxovid XBB.1.5 received marketing authorisation in the UK and in Singapore.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The MAH states that no actions were taken for safety reasons during the reporting interval.

1.3.2. Changes to reference safety information

The reference safety information (RSI) in effect at the beginning of the reporting interval was the company core data sheet (CCDS) version 9.0, dated 19 December 2023. During the reporting interval, the CCDS version 9.0 was updated to version 10.0 (effective date 30 May 2024) to remove tinnitus from the adverse reactions from post-marketing experience in section 4.8.2 and to add information on the JN.1/2024-2025 formula and prefilled syringe presentation.

Table 4: Summary of changes to the CCDS during the reporting interval (PSUR p. 28)

Location of Change	Summary of Changes
Section 1.2 – Common / Proper Name	Reference to INN removed; information about JN.1/2024-2025 Formula added to names list
Section 2 – Qualitative and Quantitative Composition	Completed missing information on active substance composition. Information about single-dose/multidose vials and single-dose pre-filled syringe added according to EMA-proposed product information. Information on JN.1 composition added. Additional text box on spike protein added. Note to local label preparer box on circulating strain added.
Section 4.2.1 – Dosing and Schedule	Information on JN.1 added. Alternate text box on 2-dose regimen added.
Section 4.6.1 – Pregnancy	JN.1 added to product reference.
Section 4.8.2 – Post-marketing experience	JN.1 added to product reference. Table 2: Deleted rows related to Ear and Labyrinth disorders and Tinnitus.
Section 6.3 – Shelf Life/Storage	Extended information with respect to single-dose vial and pre-filled syringe presentations.
Section 6.4 – Special Precautions for Storage	Pre-filled syringe presenation added.
Section 6.5 – Nature and Contents of Container	New single-dose vial and pre-filled syringe presentations added.
Section 6.6 – Instructions for Use/Handling	Extended information with respect to single-dose vial and pre-filled syringe presentations. Note to Local Labelling Preparer boxes added on storage deviation from EU labelling.

The MAH notes that no safety variations were submitted during the reporting interval.

Rapporteur assessment comment:

During the reporting interval, the RSI was updated once – from CCDS version 9.0 to CCDS version 10.0. The removal of tinnitus as a possible adverse reaction is considered appropriate as there was insufficient evidence to suggest a causal relationship between the vaccine and the development of tinnitus (see procedure EMEA/H/C/PSUSA/00010972/202306).

Based on the information provided in this PSUR, the MAH does not make any proposals in terms of new safety information and key risk minimisation recommendations.

1.3.3. Estimated exposure and use patterns

Clinical trial exposure

Novavax COVID-19 vaccines include the monovalent vaccines prototype (NVX-CoV2373; n = 46,685 participants exposed in clinical trials), BA.1 (NVX-CoV2515; n = 347), BA.5 (NVX-CoV2540; n = 297) and XBB.1.5 (NVX-CoV2601; n = 670), the bivalent vaccines prototype + BA.1 (NVX-CoV2373 + NVX-CoV2515) (n = 269), prototype + BA.5 (NVX-CoV2373 + NVX-CoV2540) (n = 259) and prototype + XBB.1.5 (NVX-CoV2373 + NVX-CoV2601), as well as the COVID-19 and influenza combination (CIC) vaccine prototype (NVX-CoV2373) + qNIV (quadrivalent nanoparticle influenza vaccine) (n = 1,422 participants exposed in clinical trials). A total of 5,075 participants were exposed to blinded treatment, and 8,460 subjects were exposed to placebo. The MAH presents cumulative exposure data by age and sex (PSUR Tables 4 and 5, p. 31) and by racial group (PSUR Table 6, p. 32). A total of 2,157 individuals from 12 to under 18 years of age were exposed to the prototype vaccine and 400 to blinded treatment. Participants under 12 years of age received blinded treatment only (< 24 months, n = 1,206; 2 – < 6 years, n = 1,216; 6 – < 12 years, n = 1,260), and 6,436 subjects older than 65 years received the different COVID-19 vaccines.

Rapporteur assessment comment:

PSUR Table 3 (p. 30) does not list any subjects who were exposed to the bivalent vaccine prototype + XBB.1.5 in clinical trials, so an exposure of zero participants may be assumed. In this PSUR, the MAH presents the data on age, sex and race in an aggregated form across clinical studies, which is endorsed. According to the data provided, predominantly adults were included in clinical trials with the vaccines (18 – 65 years, n = 42,349 including participants exposed to blinded treatment and n = 147 subjects from study 2019nCoV-312 counted twice). The sex distribution of the participants is quite balanced, and the majority of subjects are described as White or Caucasian (n = 38,313 excluding subjects exposed to placebo).

Post-authorisation exposure

Nuvaxovid: According to the MAH, during the reporting interval, no doses were distributed and 5,797 doses were administered, thereof 4,219 Nuvaxovid doses in Australia, Canada, and Japan and 1,578 Covovax doses in India. Cumulatively, 124,790,110 doses (115,455,860 Nuvaxovid and 9,334,250 Covovax doses) were distributed and 2,989,177 doses were administered (2,934,244 Nuvaxovid doses administered in Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, UK, and US and 54,933 Covovax doses administered in India).

Nuvaxovid XBB.1.5: During the reporting interval, 9,009,590 doses were distributed and 1,048,691 doses were reported to have been administered in Canada, EU, South Korea, Taiwan and US. Cumulatively, 18,101,000 doses were distributed and 1,201,601 doses were administered (Canada, EU, South Korea, Taiwan and US). As of the data lock point (DLP) of this report, administration information from other countries/regions was not yet available to the MAH.

Table 5: Overall summary of administration and distribution of Novavax COVID-19 vaccines (PSUR Table 7, p. 33)

Timeframe	Nuvaxovid **		Nuvaxovid XBB.1.5 **		Novavax COVID-19 Vaccines	
	Administered	Distributed	Administered	Distributed	Administered	Distributed
Interval *	5,797	0	1,048,691	9,009,590	1,054,488	9,009,590
Cumulative	2,989,177	124,790,110	1,201,601	18,101,000	4,190,778	142,891,110

* Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source as indicated in Table 42.

** Includes Novavax and SIIPL products corresponding to the original and updated Novavax COVID-19 vaccines.

Rapporteur assessment comment:

According to Table 7 (PSUR p. 33), 5,797 out of a cumulative total of 2,989,177 Nuvaxovid doses (0.2%) were administered during the reporting interval. The number of doses cumulatively administered and provided in the last PSUR (n = 2,982,912) plus the doses administered during this reporting interval (n = 5,797) does not exactly match the total number of doses specified in this report, but this may be attributable to the available data sources. In addition, 1,048,691 out of a cumulative total of 1,201,601 Nuvaxovid XBB.1.5 doses (87.3%) were administered during the reporting interval.

The MAH's statement on distributed doses is not comprehensible – if no Nuvaxovid doses were distributed during the reporting interval, the cumulative number of distributed doses should not differ between this (n = 124,790,110) and the previous PSUR (n = 115,971,670). The MAH is kindly asked to clarify this discrepancy.

There is still no breakdown by dose in this PSUR. However, it can be assumed that most doses are currently applied as a booster. In its responses relating to the issues to be addressed in the next PSUR (see procedure EMEA/H/C/PSUSA/00010972/202312), the MAH points out that post-authorisation use in the elderly, paediatric, pregnant and breastfeeding, immunocompromised, frail patients with comorbidities and in patients with autoimmune or inflammatory disorders is included in sections 15.3.9,

16.3.5.1, 16.3.5.2, 16.3.5.3 and 16.3.5.4 of the PSUR. This is noted, although the EMA GVP guideline module VII (EMA/816292/2011 Rev 1*) addresses post-authorisation use in special populations under PSUR sub-section *Cumulative and interval patient exposure from marketing experience*.

1.3.4. Data in summary tabulations

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 was used for the coding of serious adverse events (SAEs) and adverse drug reactions (ADRs).

Cumulative summary tabulations of serious adverse events from clinical trials

In PSUR Appendix 5 (PSUR pp. 313-362), the MAH presents cumulative summary tabulations of treatment-emergent SAEs from MAH-sponsored interventional clinical trials of NVX-CoV2373, NVX-CoV2515, NVX-CoV2540 and NVX-CoV2601 from the development international birth date (DIBD) 23 April 2020 to the DLP (19 December 2023) of the periodic benefit-risk evaluation report (PBRER).

Cumulative and interval summary tabulations from post-authorisation data

Interval and cumulative counts of serious and non-serious adverse reactions for all spontaneous, regulatory authority, literature sources, and serious adverse reactions from non-interventional studies are provided in Appendix 6A (PSUR pp. 364-422) and 6B (PSUR pp. 423-439) for Nuvaxovid and Nuvaxovid XBB.1.5, respectively.

Table 6: Overview of interval and cumulative individual case safety reports (ICSRs) and adverse events (AEs; PSUR p. 36)

Parameters		Nuvaxovid (Cumulative administered doses = 2,989,177)		Nuvaxovid XBB.1.5 (Cumulative administered doses = 1,201,601)	
		Interval [1]	Cumulative	Interval [1]	Cumulative
Number of ICSRs		174 (106 initial, 68 follow-up)	5,154	355 (336 initial, 19 follow-up)	498
Serious ICSRs (including fatal)		44	1,009	55	66
Non-Serious ICSRs		130	4,145	300	432
Fatal ICSRs		3 (1 initial, 2 follow-up)	34	8 (7 initial, 1 follow-up)	8
Number of AEs		680	18,386	1,472	1,878
Serious AEs		184	2,846	157	169
Non-serious AEs		496	15,540	1,315	1,709
Number of ICSRs classified by age group	Foetus [2]	–	1	1	2
	Neonate [2]	–	3	1	1
	Infant	–	1	–	–
	Child	–	8	–	2
	Adolescent	1	66	3	5
	Adult	93	3,732	108	160
	Elderly	29	729	65	97
	Unknown	51	614	177	231

[1] Includes both initial and follow-up counts

[2] Secondary exposure during pregnancy

Aggregate adverse event data from South Korea: In PSUR section 6.3.2, the MAH provides aggregate safety data from the COVID-19 Vaccine Safety Report (Week 169), covering the period from 26 February 2021 to 25 May 2024. According to PSUR Table 8 (p. 34), a cumulative total of 974,574 Nuvaxovid doses and 12,311 Nuvaxovid XBB.1.5 doses were administered in South Korea up to 19 June 2024. For these vaccines, 1,296 and 4 AEs were reported, respectively. The most frequently reported symptoms suspected to be AEs were myalgia (n = 278), headache (n = 258), dizziness (n = 180), chest pain (n = 172), allergic reaction (n = 170), and vaccination site pain, rash, swelling within 3 days of vaccination (n = 137). A cumulative total of 13 cases reported fatal outcomes.

Rapporteur assessment comment:

The MAH now presents the summary tabulations aggregated for all clinical studies together, which is basically supported. As most participants were exposed to the prototype NVX-CoV2373, the majority of SAEs presumably are attributable to this vaccine. Nevertheless, a breakdown by vaccine would be useful in order to detect any differences in the SAE profile. The MAH is therefore kindly asked to provide an analysis by vaccine in subsequent PSURs; events from different studies involving the same vaccine should be aggregated unless this is considered inappropriate by the MAH and justified accordingly. Appendix 5 lists a total of 3,015 SAEs across all treatment arms – 2,498 for the study product (test drug), 2,303 for placebo/vehicle, 9 for the comparator product (reference drug), and 217 for the blinded treatment. The system organ classes (SOCs) under which SAEs were most frequently reported were Infections and infestations (n = 711), Cardiac disorders (n = 326) and Injury, poisoning and procedural complications (n = 278).

In this PSUR, adverse reactions from post-authorisation data sources are presented separately for Nuvaxovid and Nuvaxovid XBB.1.5. This is endorsed.

Appendix 6A lists a cumulative total of 18,157 spontaneously reported events for Nuvaxovid, thereof 2,838 serious and 15,319 non-serious events (reporting interval, n = 184 serious and n = 459 non-serious events). In addition, 7 serious events were reported cumulatively from non-interventional post-marketing study and other solicited sources (reporting interval, n = 0 serious events). The most frequently involved MedDRA SOCs were General disorders and administration site conditions (n = 5,183 spontaneous reports; preferred term [PT] Fatigue, n = 690), Nervous system disorders (n = 3,056; PT Headache, n = 1,042), Musculoskeletal and connective tissue disorders (n = 1,971; PT Myalgia, n = 680), Gastrointestinal disorders (n = 1,195; PT Nausea, n = 464), and Skin and subcutaneous tissue disorders (n = 1,055; PT Rash, n = 293). These frequently reported PTs are all listed in SmPC section 4.8 with the frequency *very common* (Headache, Nausea, Myalgia, Fatigue) or *uncommon* (Rash).

Appendix 6B lists a cumulative total of 1,169 spontaneously reported events for Nuvaxovid XBB.1.5, thereof 167 serious and 1,002 non-serious events (reporting interval, n = 156 serious and n = 615 non-serious events). In addition, 2 serious events were reported cumulatively from non-interventional post-marketing study and other solicited sources (reporting interval, n = 1 serious event). The most frequently involved MedDRA SOCs were General disorders and administration site conditions (n = 303 spontaneous reports), Nervous system disorders (n = 159), Injury, poisoning and procedural complications (n = 140), Musculoskeletal and connective tissue disorders (n = 116), and Respiratory, thoracic and mediastinal disorders (n = 88).

For Nuvaxovid, 174 (106 initial, 68 follow-up) of a cumulative total of 5,154 ICSRs (3.4%) and 680 of 18,386 AEs (3.7%) were received during the reporting interval. In addition, 355 (336 initial, 19 follow-up) of a cumulative total of 498 ICSRs, as well as 1,472 of 1,878 AEs, were received during the reporting interval for Nuvaxovid XBB.1.5. With regard to the doses administered, this corresponds to reporting rates of 0.17 (5,154/2,989,177) and 0.04 (498/1,201,601) per 100 vaccinations for Nuvaxovid and Nuvaxovid XBB.1.5, respectively.

Based on the data presented, no new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

Clinical trials

During the reporting interval, two parts of a 4-part clinical trial (study 2019nCoV-301 adult main and adult booster), one part of a 2-part clinical trial (study 2019nCoV-311 Part 1) and one other clinical trial (study 2019nCoV-505) were completed. Also, seven clinical trials (of which one is a 4-part clinical trial and one is a 2-part clinical trial) were ongoing: 2019nCoV-205, 2019nCoV-301 (adolescent main and adolescent booster), 2019nCoV-311 part 2, 2019nCoV-312, 2019nCoV-313 (parts 1 and 2), 2019nCoV-314 and 2019nCoV-503.

Completed clinical trials

Study 2019nCov-301 adult main and adult booster – a phase 3, multinational, multicentre, randomised, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant (also referred to as NVX-CoV2373) in adult participants ≥ 18 years of age in the US and Mexico (adult main study) with a paediatric expansion in adolescents 12 to < 18 years of age and a booster amendment and second booster vaccination sub-study

The study was initiated on 27 December 2020 (first participant screened) and completed enrolment into the initial vaccination period on 18 February 2021. The blinded crossover vaccination period was initiated on 20 April 2021, and the first and second booster vaccination periods were initiated on 13 December 2021 and 19 September 2022, respectively. The date of the last participant, last visit for the final (24-month) analysis was 10 Apr 2023, with database lock on 20 December 2023. The MAH notes that safety data were updated cumulatively through the end of study analysis and that no new safety signals were identified.

Efficacy: A two-dose primary regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart in the initial vaccination period, met the prespecified study success criterion of the primary efficacy outcome measure versus placebo in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in seronegative (to SARS-CoV-2) adult participants.

Immunogenicity: A two-dose regimen of NVX-CoV2373 markedly increased wild-type virus (ancestral Wuhan strain) neutralising antibody, serum IgG antibody, hACE2 receptor binding inhibition antibody levels relative to placebo in adult participants regardless of baseline serostatus. Greater immune responses were observed in younger adult participants (18 to < 65 years of age) than in older adult participants (≥ 65 years of age) but with high seroconversion rates across the age groups. A single booster dose, administered at a minimum of 6 months after the primary series of NVX-CoV2373, elicited robust immune responses at 28 days after booster vaccination that were higher than those reported at 14 days after primary series vaccination. Sustained immune responses were observed through 240 days after the booster dose, and immune responses after a second booster dose were comparable to those following the first booster.

Safety: The median duration of safety follow-up was 2.5 months after the second vaccination in the initial vaccination period, 8.4 months after second vaccination in the blinded crossover vaccination period, and 11.9 months after the booster dose. According to the MAH, a two-dose regimen of NVX-CoV2373 followed by a booster dose administered ≥ 6 months after completion of the primary series was well tolerated and had an acceptable safety profile. During the initial vaccination period, NVX-CoV2373 recipients reported

higher frequencies and intensities of solicited injection site and systemic treatment emergent adverse events (TEAEs) than placebo recipients, especially after the second vaccination. This trend was observed in both age cohorts, 18 to < 65 years of age and ≥ 65 years of age, with lower frequencies and intensities of solicited injection site and systemic TEAEs in the older age cohort. Tenderness and pain were the most frequently reported local injection site TEAEs, and fatigue, headache, myalgia, and malaise were the most frequently reported systemic TEAEs. Following administration of a booster dose, the frequency of solicited injection site and systemic TEAEs was similar to that observed following the second dose; however, although most TEAEs remained grade 1 or 2 in severity following the booster dose, there was an increase in the frequency of grade ≥ 3 TEAEs. During the initial vaccination period, SAEs were reported for 1.2% of NVX-CoV2373 recipients and 1.3% of placebo recipients. Within the 11.9 months of median follow-up following the booster dose, 3.0% of participants reported SAEs.

Study 2019nCoV-311 part 1 – a multi-part, phase 3, randomised, observer blinded study to evaluate the safety and immunogenicity of Omicron subvariant and bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines – 951 participants

Study part 1 evaluated a single booster dose of NVX-CoV2515 and NVX-CoV2373 alone and bivalent prototype and Omicron subvariant vaccine (NVXCoV2373 + NVX-CoV2515) in previously vaccinated adults 18 to 64 years of age. It was initiated on 31 May 2022 (first participant screened) and completed enrolment on 17 July 2022. Participants were previously vaccinated with two (groups A and B) or three (groups C, D, and E) doses of the Moderna and/or Pfizer-BioNTech prototype vaccines. The final CSR summarised the results of part 1 through the end of the study with a data extraction date of 18 October 2023.

Immunogenicity: The primary objective of the study was met, achieving both co-primary endpoints needed to demonstrate that the Omicron BA.1 specific vaccine (NVX-CoV2515) produced a superior antibody response to the Omicron BA.1 subvariant when compared to the prototype vaccine (NVX-CoV2373) at day 14. The secondary objective aiming to conclude non-inferiority of the bivalent vaccine with the strain-matched monovalent vaccine failed to meet endpoint criteria for success. Overall antibody responses at day 28 were similar in participants previously vaccinated with two or three doses of the Moderna and/or Pfizer-BioNTech prototype vaccines across the various assays and SARS-CoV-2 variants analysed. The durability of immune responses through day 240 was more robust in participants with three prior vaccinations than those with two prior vaccinations.

Safety: The incidence of solicited local and systemic reactogenicity reported in this study was consistent with the reactogenicity seen in previous studies with NVX-CoV2373. Most solicited local injection site and systemic TEAEs were grade 1 or grade 2 in intensity, with grade 3 local injection site TEAEs reported in less than 2% of participants and grade 3 systemic TEAEs reported in ≤ 5% of participants.

Study 2019nCoV-505 – a phase 2, randomised, observer-blinded study to evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in people living with human immunodeficiency virus (PLWH) – 383 participants

The MAH notes that the study operated under the hypothesis that an expanded interval between vaccinations or an additional immunising exposure to vaccine will establish an optimal vaccine regimen that would mount an immune response in PLWH comparable to that seen in human immunodeficiency virus (HIV)-negative adults regardless of baseline serostatus. However, the hypothesis could not be evaluated because the majority of the study population (i.e., between 82.8% and 91.5% of participants depending on treatment group) was baseline seropositive.

Immunogenicity: A standard two-dose primary vaccination series with NVX-CoV2373 (administered at days 0 and 21) in PLWH induced a robust immune response comparable to that seen for HIV-negative participants who received the same treatment regimen. Immune responses were generally lower post

vaccination after a modified two-dose vaccination series (vaccination on Days 0 and 70) indicating that an expanded interval between vaccinations did not appear to provide an optimal vaccine regimen relative to either a standard two-dose primary vaccination series or a standard two-dose vaccination series plus a third vaccination. Immune responses for PLWH with well-controlled and less-well-controlled HIV infection were comparable and equally robust and followed the same pattern of responses as those seen for the population as a whole.

Safety: The majority of participants across all treatment groups overall did not experience solicited local or systemic TEAEs following vaccination. Few participants reported grade 3 (i.e., severe) solicited local or systemic events (ranges of 1.2 to 2.4% and 1.8 to 4.9%, respectively). Pain and tenderness were the most frequently reported solicited local TEAEs and headache and muscle pain were the most frequently reported solicited systemic TEAEs after each vaccination across all subsets of participants.

Ongoing clinical trials

During the reporting interval, interim analyses became available for the ongoing clinical trials 2019nCoV-311 part 2 and 2019nCoV-313 part 1.

Study 2019nCoV-311 – a multi-part, phase 3, randomised, observer blinded study to evaluate the safety and immunogenicity of Omicron subvariant and bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines – **part 2**

Immunogenicity: Neutralising antibody (NAb) responses against the Omicron BA.5 subvariant pseudovirus and the Omicron XBB.1.5 pseudovirus were more robust at all time points after both booster vaccinations with the bivalent vaccine versus NVX-CoV2373 while NAb responses against the ancestral (Wuhan) pseudovirus were similar for the bivalent vaccine versus NVX-CoV2373 vaccine. The MAH notes that the extent to which responses were increased with NVX-CoV2540 and the bivalent vaccine versus NVX-CoV2373 were similar, suggesting that NVX-CoV2540 was the main active component in the bivalent vaccine.

Safety: According to the MAH, NVX-CoV2540, NVX-CoV2373, and NVX-CoV2373 + NVX-CoV2540 were well tolerated with an acceptable safety profile after initial and second booster vaccination in adult participants who had previously received ≥ 3 vaccinations of Moderna and/or Pfizer-BioNTech prototype mRNA COVID-19 vaccines.

Study 2019nCoV-313 – a 2-part phase 2/3 open-label study to evaluate the safety and immunogenicity of an XBB.1.5 (Omicron subvariant) SARS-CoV-2 rS vaccine booster dose in previously mRNA COVID-19 vaccinated and baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants – **part 1**

Part 1 of study 2019nCoV-313 was initiated on 07 September 2023 (first participant screened) and completed enrolment on 08 September 2023. The co-primary objectives were (i) to determine if NVX-CoV2601 booster induced superior antibody responses to the Omicron XBB.1.5 subvariant compared to the antibody responses of a historical control of NVXCoV2373 and (ii) to determine if NVX-CoV2601 booster induced non-inferior seroresponse rates (SRRs) compared to SRRs of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations.

Immunogenicity: Both co-primary endpoints were achieved. The SRRs of NVX-CoV2601 and the historical control NVX-CoV2373 were 64.3% (95% confidence interval [CI]: 58.6, 69.6) versus 7.0% (95%CI: 4.1, 11.2), respectively, at day 28.

Safety: Solicited local injection site and systemic TEAEs were reported in 189 (56.9%) and 158 (47.6%) participants, respectively, with most participants reporting grade 1 or grade 2 events. Higher frequencies of solicited local injection site and systemic TEAEs were reported in participants 18 to 54 years of age (64.2% and 51.7%, respectively) than in participants ≥ 55 years of age (48.7% and 42.9%,

respectively). The MAH states that the data demonstrated no obvious change in the safety profile of SARS-CoV-2 rS protein subunit vaccines with XBB.1.5 strain change.

Long-term follow-up

The MAH notes that most company-sponsored clinical trials collect up to one year of follow-up data for enrolled participants, except Study 2019nCoV-301 which collects up to two years of follow-up data. As of the DLP, no new safety information became available from long-term follow-up in company-sponsored clinical trials.

Other therapeutic use of medicinal product

According to the MAH, no programs involving other therapeutic uses of Nuvaxovid or Nuvaxovid XBB.1.5 were ongoing during the reporting interval.

New safety data related to fixed combination therapies

During the reporting interval, there was one completed company-sponsored clinical trial involving CIC vaccine, phase 2 study, 2019nCoV-CIC-E-201, and there were no significant safety findings from the study as of DLP.

Non-interventional studies

During the reporting interval, three company-sponsored post-authorisation safety studies (PASSs) and four company-sponsored post-authorisation efficacy studies (PAESs) were ongoing. Two company-sponsored PAESs were completed. There was also one collaborative research PAES ongoing during the reporting interval. The MAH notes that no new findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported from any non-interventional studies.

Other clinical trials

During the reporting interval, there were five ongoing and four completed investigator-initiated studies, and one completed license partner-sponsored study. The MAH states that no significant safety findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported.

In Study TAK-019-3001, extension part, 129 participants received a second booster vaccination of NVX-CoV2373. This second booster dose as a heterologous vaccine elicited rapid and robust immune responses for serum IgG antibody and serum neutralising antibody, which addressed waning immunity after the first booster dose of NVX-CoV2373 following the primary series of Comirnaty injection.

Medication errors

Nuvaxovid. Using its pre-specified search strategy, the MAH retrieved 10 initial and two follow-up individual case safety reports (ICSRs) for the reporting interval. A cumulative total of 268 ICSRs were retrieved and included 333 AEs. The most frequently reported PTs (n ≥ 20) were Expired product administered (n = 51), Incomplete course of vaccination (n = 36), Inappropriate schedule of product administration (n = 33), Interchange of vaccine products (n = 30), Vaccination error (n = 23), Product administration error (n = 21), and Product administered to patient of inappropriate age (n = 20).

Nuvaxovid XBB.1.5. The MAH retrieved 40 initial and two follow-up ICSRs for the reporting interval. A cumulative total of 83 ICSRs were retrieved and included 123 AEs. The most frequently reported PTs (n ≥ 10) were Product storage error (n = 38), Expired product administered (n = 37), and Product administration error (n = 28). The MAH notes that during the reporting interval, a disproportionate number of reports (n = 41 ICSRs) falling under the MedDRA high level term (HLT) Product administration errors and issues was detected with a majority of ICSRs reporting events of Expired product administered (n = 28). All reports were non-serious. No associated quality complaints were received, there was no indication of product label or instructions for use concerns, and no signal was generated.

Non-clinical data

During the reporting interval, there were eight completed and 15 ongoing non-clinical studies for SARS-CoV-2 rS. According to the MAH, there were no significant safety findings from non-clinical studies that impacted the benefit-risk profile of SARS-CoV-2 rS.

Literature

The MAH conducted weekly literature searches using EMBASE and reviewed a total of 91 publications of which 17 presented new or significant findings (safety or safety and immunogenicity, n = 8; efficacy/effectiveness and/or immunogenicity, n = 9, summarised in PSUR section 17.2.2). In PSUR section 11, the MAH summarises the eight publications on safety/immunogenicity; its review did not identify any new safety findings that impacted the overall benefit-risk balance of Nuvaxovid or Nuvaxovid XBB.1.5.

A retrospective study (Clothier HJ et al, doi: https://doi.org/10.1101/2024.03.17.24304409) describes 356 spontaneously reported AEs following administration of 102,946 Nuvaxovid doses in Australia. Reporting rates were higher after dose 1 than after dose 2 (rate ratio [RR] 1.5, p = 0.0008), after a primary series than a booster group (RR 2.4, p < 0.0001), and in females than in males (RR 1.4, p < 0.01). Serious AEs included events of chest pain (n = 76), myocarditis (n = 2) and pericarditis (n = 20).

Other periodic reports

The MAH lists six summary safety reports, with reporting intervals between 01 December 2023 and 31 May 2024, submitted in the US, and one PSUR submitted for Covovax in South Africa. It states that no new significant safety related issues were identified from these reports which could change the conclusion of this PBRER.

Rapporteur assessment comment:

PSUR Appendix 8 lists two out of three completed company-sponsored interventional clinical trials (2019nCoV-505 and 2019nCoV-311 part 1; Table 34, pp. 448-449) and four out of five ongoing investigator-initiated studies (Table 37, pp. 461-462). Besides, only three and not four ongoing company-sponsored PAESs are listed in Appendix 9 (PSUR p. 465). In subsequent PSURs, the MAH is kindly asked to harmonise the information provided in the core report and the appendices.

In the preprint article authored by Clothier et al, a total of 76 serious events of chest pain were described. However, in the EU SmPC for Nuvaxovid/Nuvaxovid XBB.1.5, chest pain is only mentioned in the context of myocarditis and pericarditis.

Overall, the information presented by the MAH does not change the known safety profile of Nuvaxovid and Nuvaxovid XBB.1.5.

1.3.6. Lack of efficacy in controlled clinical trials

The MAH states that during the reporting interval and cumulatively, no data suggesting lack of efficacy that would constitute a significant risk to the study population was obtained from controlled clinical trials.

1.3.7. Late-breaking information

The MAH did not receive any late breaking information with reference to Nuvaxovid's safety, efficacy and effectiveness after the DLP of this PBRER.

Rapporteur assessment comment: According to the MAH, no safety, efficacy and effectiveness findings arose after the DLP of this PSUR.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 7: Summary of safety concerns at the beginning of the reporting interval (PSUR pp. 141-142)

Important identified risk	Myocarditis and/or pericarditis
Important potential risk	Vaccine associated enhanced disease, including vaccine-associated enhanced respiratory disease
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

2.2. Signal evaluation

Table 8: Tabular overview of signals: new, ongoing or closed during the reporting interval 20 December 2023 to 19 June 2024 (excerpt from PSUR Appendix 7, Table 33, pp. 440-447)

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason and summary	Method of signal evaluation	Action(s) taken or planned
Tinnitus	27 September 2023	Closed	01 April 2024	PSUR assessment report (procedure EMEA/H/C/PSUSA/00010972/202306) dated 11 January 2024 and US FDA comment to Novavax 9-27-23	Health authority request	Signal evaluation report submitted with PBRER No.05	Tinnitus will be removed from the Nuvaxovid CCDS and will remain in the post-authorisation section of the Australian product information (section

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason and summary	Method of signal evaluation	Action(s) taken or planned
				XBB15-hcp-fact-sheet_EUA28237_130 dated 27 September 2023			4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance including information regarding plausible mechanisms.
Migraine	25 January 2024	Closed	01 April 2024	Health authority query (TGA)	Health authority request	Provided in signal evaluation report submitted with PBRER No.05	Continue routine surveillance
Tachycardia	21 March 2024	Closed	07 May 2024	Information request 21 March 2024 for SSR No.26	Health authority request (US FDA)	Provided in signal evaluation report submitted with PBRER No.05	Continue routine surveillance

During the reporting interval, the signals of migraine and tachycardia were validated following health authority requests from the Therapeutic Goods Administration (TGA) and US Food and Drug Administration (FDA), respectively. The MAH refuted both signals upon evaluation. Further, the final disposition of the previously validated signal of tinnitus was updated to refuted during the reporting interval in response to US FDA and European Medicines Agency (EMA) reviews and assessments. Tinnitus has been removed from the CCDS version 10.0 (section on adverse reactions from post-marketing experience) and will remain in section 4.8 of the Australian product information.

Signal evaluation report on migraine with use of Nuvaxovid/Nuvaxovid XBB.1.5

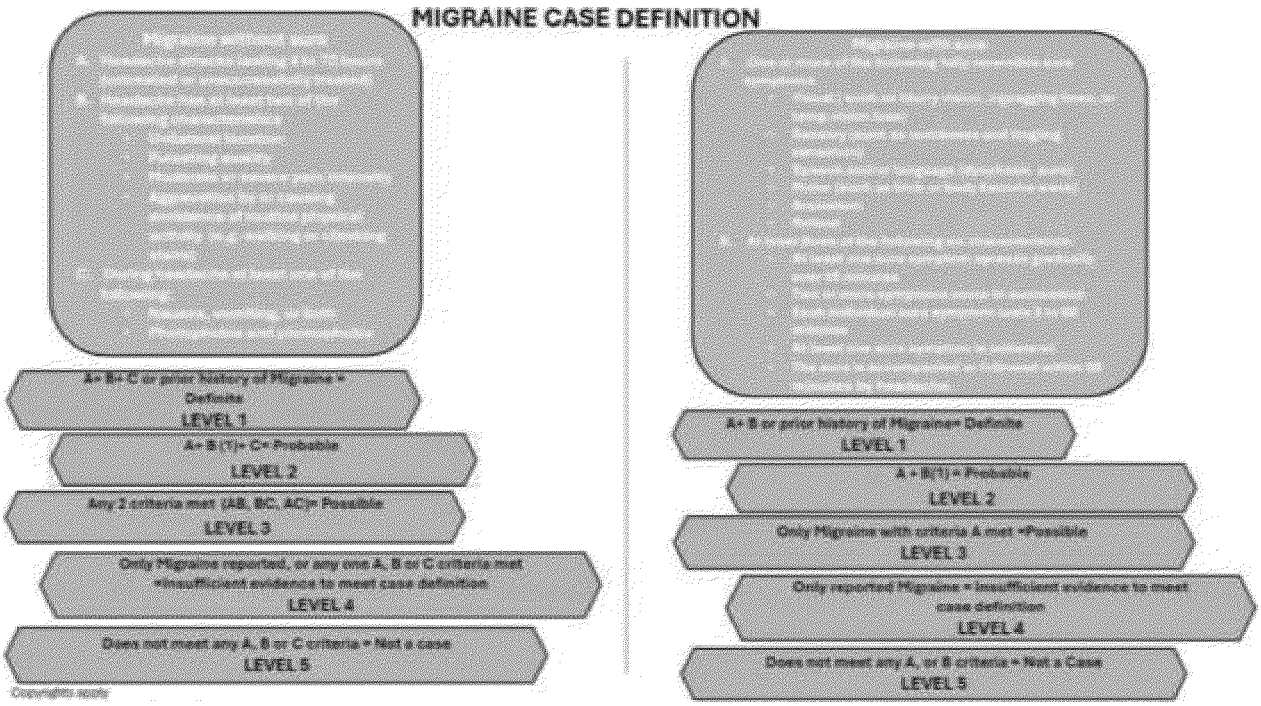
In PSUR Appendix 21 (pp. 702-791), the MAH provides its signal evaluation report for migraine, dated 27 March 2024. The report encompasses information available to the MAH, with cut-off dates for clinical studies ranging from 28 July 2021 to 31 May 2023, and with the cut-off date 16 February 2024 for post-authorisation data. The safety signal had been identified by the Australian TGA.

Studies estimate the incidence of episodic migraine to range from 399 to 2,300 per 100,000 person-years. The prevalence of episodic migraine is approximately 12%, and the global chronic migraine prevalence is estimated to be 1.4-2.2%. The MAH notes that in the context of COVID-19 vaccination, the published literature is limited to vaccination-related headache, without necessarily meeting the criteria of migraine disorder. A meta-analysis of studies that reported headache following SARS-CoV-2 vaccination among 22% of first-dose recipients and 29% of second dose participants, indicated that these rates were more than double those in the placebo groups. The duration and intensity of post-vaccination headache has been shown to be significantly longer among patients with a history of migraine compared to those without. Migraine is not included in the Nuvaxovid CCDS version 9.0 (effective 19 December 2023).

Methods

- Clinical trial data. The Nuvaxovid clinical safety analysis dataset (five completed and four ongoing clinical studies; 31,479 and 19,879 adult participants, respectively, in the NVX-CoV2373 and placebo groups and 1,487 and 745 adolescent participants respectively, in the NVXCoV2373 and placebo groups) was searched for AEs under the MedDRA HLT Migraine headaches within 7 days of any dose.
- Post-authorisation data. A cumulative search of the post-authorisation safety database was performed with the MedDRA HLT Migraine headaches with a DLP of 16 February 2024.
- Case definition. The MAH modified the diagnostic criteria set forth by the International Classification of Headache Disorders (ICHD-3) to allow for inclusion of events that otherwise might not have met the definition of migraine.

Figure 1: Case definition for migraine (PSUR p. 791)



- Observed to expected analysis was performed with multiple risk windows.
- Disproportionality analysis. Data mining reports from the US Vaccine Adverse Event Reporting System (VAERS) and EudraVigilance Data Analysis System (EVDAS) databases were reviewed.
- Literature. The MAH searched several databases for literature on Nuvaxovid and migraines.

Results – Clinical trial data

A total of 20 AEs (thereof one serious) of migraine were reported among the NVX-CoV2373 recipients within 7 days of any dose for the overall analysis set (n = 30,070 individuals immunised). The MAH did not detect any difference across the vaccine and placebo groups for migraine when examined as a combined term (migraine and migraine with aura) and when evaluated individually.

Table 9: Summary of migraine (by MedDRA HLT) reported 7 days post any dose in adult population (PSUR p. 718)

Pre-Crossover	Vaccine (n, %, 95% CI) N=30070	Placebo (n, %, 95% CI) N=19879	Risk Difference (Vaccine-Placebo) (%, 95% CI)
Any AE of Migraine (by MedDRA HLT)	16 (0.05%), (0.03, 0.09)	9 (0.05%), (0.02, 0.09)	0.03% (-0.01, 0.07)
Migraine	16 (0.05%)	8 (0.04)	-0.00 (-0.01, 0.00)
Migraine with aura	0	1 (<0.01)	
Post-Crossover Period	**Placebo to Vaccine (n, %, 95% CI) N=9634**	**Vaccine to Placebo (n, %, 95% CI) N=18584**	**Risk Difference (Vaccine-Placebo) (%, 95% CI)**
Any AE of Migraine (by MedDRA HLT)	3 (0.03), (0.01, 0.09)	4(0.02), (0.01, 0.06)	0.01 (-0.03, 0.05)
Migraine	3 (0.03)	3 (0.02)	0.02 (-0.02, 0.06)
Migraine with aura	0	1 (<0.01)	-0.00 (-0.01, 0.00)
Booster Period	**Vaccine (n, %, 95% CI) N=16945**	**Placebo**	**Risk Difference**
Any AE of Migraine (by MedDRA HLT)	1(<0.01), (0.00, 0.03)	N/A	N/A
Migraine	1(<0.01)	N/A	N/A

Results – Post-authorisation safety data

Nuvaxovid: The MAH retrieved 78 ICSRs which included 81 AEs (thereof 20 serious) coded to the MedDRA PTs Migraine (n = 76), Ophthalmic migraine (n = 2), Migraine with aura (n = 1), Typical aura with headache (n = 1), and Vestibular migraine (n = 1).

Nuvaxovid XBB.1.5: The MAH retrieved 7 ICSRs which included 8 non-serious AEs coded to the MedDRA PTs Migraine (n = 7) and Migraine with aura (n = 1).

The ICSRs were adjudicated against the case definition and causality was assessed using the WHO Causality Assessment of an Adverse Event Following Immunisation (AEFI).

Table 10: Event characteristics of reports retrieved for the MedDRA HLT Migraine headaches (excerpt from PSUR pp. 720-721)

		Nuvaxovid	Nuvaxovid XBB.1.15
Reports Retrieved		78	7
Adjudication Against Case Definition	Level 1	12	3
	Level 2	0	0
	Level 3	16	1
	Level 4	48	3
	Level 5	2	0
PTs retrieved by the search strategy*	Migraine	75	7
	Ophthalmic migraine	2	0
	Migraine with aura	1	1
	Vestibular migraine	1	0
	Typical aura without headache	1	0
Outcome (for PTs retrieved by the search strategy)	Not Recovered/Not Resolved	39	3
	Recovered/Resolved	19	3
	Unknown	12	1
	Recovering/Resolving	6	0
	Recovered with Sequelae	3	0
Time to onset	1 day (within 24 hours of vaccination)	27	2
	2-7 days	27	2
	8-30 days	5	2
	>1 month	6	0
	UNK	13	1

The MAH lists all 85 cases in a table, with information on reported MedDRA PTs, time to onset, outcome, diagnostic evidence (sponsor case definition) and WHO sponsor causality assessment.

In addition, the MAH queried its global safety database for ICSRs reported in individuals who had a medical history of any terms that fell under MedDRA HLT Migraine headaches. A total of 39 ICSRs were retrieved, thereof 31 with Nuvaxovid and 8 with Nuvaxovid XBB.1.5. A total of 222 AEs were reported, involving 30 females, 7 males and 2 persons of unknown gender. The most frequently reported MedDRA PTs were Fatigue (n = 10 events), Migraine (n = 8), Headache (n = 8), Pain in extremity (n = 7) and Nausea (n = 6).

Results – Observed to expected (O/E) analysis

Table 11: Post-vaccination time to event distribution for migraine AEs in the MAH's global safety database (PSUR p. 783)

Time to Event	AE Count
Unknown	19
Days 1 – 2*	46
Days 3 – 4	8
Days 5 – 7	5
Day 9+	8
Duplicate ICSRs	3

*First hour excluded. This risk window represents 1 – 24 hours post vaccination.

For its O/E analysis, the MAH employed a background rate of 1,142.5 cases per 100,000 person-years. A total of 3,659,924 doses was used to calculate the expected rate. The MAH states that the observed count was lower than the expected count for all risk windows.

Table 12: O/E calculations for the risk windows days 1-2, days 3-4 and days 5-8 (PSUR p. 784)

Risk window	Observed cases	Risk window duration [days]	Person-time (x100 K PY)	Background rate (/100 K PY)	Expected cases	O/E ratio (95% CI)
Days 1-2	65	1	0.0970	1,142.5	110.8	0.59 (0.45, 0.75)
Days 3-4	27	2	0.2024	1,142.5	231.2	0.12 (0.08, 0.17)
Days 5-8	24	3	0.3036	1,142.5	346.9	0.07 (0.04, 0.10)

Results – Disproportionality analysis of post-authorisation spontaneous data

Analyses using data from VAERS (29 December 2023; PT Migraine – EB05, 0.252, cumulative count, n = 11; PT Migraine with aura – EB05, 1.282, cumulative count, n = 1) and EVDAS (13 February 2024) do not indicate disproportionate reporting for migraine and migraine with aura.

Results – Literature

The MAH retrieved six literature articles. According to the MAH, none of these articles contributed new safety information regarding the association between Nuvaxovid and migraine headache.

Conclusion

Across the MAH's integrated safety summary, events of migraine were balanced across treatment and placebo groups. No signal has been detected quantitatively or qualitatively across the global post-authorisation safety data for new onset migraine or disease exacerbation in individuals with medical history of migraine. The MAH concludes that its comprehensive review did not identify any evidence of a causal association between Nuvaxovid and migraine beyond temporal association.

Rapporteur assessment comment:

In January 2024, a safety signal pertaining to migraine was identified by the Australian TGA. The MAH's routine pharmacovigilance activities had not indicated a signal here. The MAH's search with the MedDRA HLT Migraine headaches, as chosen for both the clinical trial dataset and the post-authorisation safety database, is considered appropriate. It covers different forms of migraine, but no other types of headache. This concept is accepted as the term migraine is well known and is often interpreted too broadly rather than too restrictively.

In the clinical studies included in the analysis, there was no obvious difference between vaccine and placebo as regards events reported within 7 days of the first two doses. For the booster period, no placebo group was available to compare. Overall, migraines were rarely observed in the MAH's clinical trial dataset, with no apparent imbalance between the vaccine and placebo groups.

From post-marketing sources, the MAH retrieved a total of 78 ICSRs for Nuvaxovid and 7 ICSRs for Nuvaxovid XBB.1.5. The MAH's development of distinct case categories (in the absence of a Brighton Collaboration case definition) and its assessment of causality according to the WHO AEFI criteria is appreciated. Events under the HLT Migraine headaches were reported more frequently by females (n = 57) than by males (n = 23) and preferably in mid adulthood, which is consistent with the epidemiology of the condition. In 29 out of 85 cases, the time to onset was within 24 hours of vaccination. The MAH categorised five cases as *consistent with causal association to immunisation*, 39 cases as *indeterminate*, 24 cases as *inconsistent with causal association to immunisation* and 17 cases as *unclassifiable*. The MAH's assessment of the cases is overall supported, although the assessor would have chosen a different

causality category in some cases. If inadequate information is available for the assessment, this corresponds more to the category *unclassifiable* than *inconsistent*. It is unclear which risk window was applied for a temporal association, and there is no comment on this in the MAH's methods section. Concerning alternative aetiologies, it is noted that although high blood pressure may provoke headaches, the severe pain associated with a migraine attack can also increase blood pressure.

The background incidence used for the O/E analyses is considered suitable. Overall, the MAH's calculations do not indicate an increased migraine incidence following vaccination, although possible underreporting was not taken into account. In the event of underreporting of 75%, for example, the O/E rate would be increased in the 1-2 days risk window.

As regards disproportionality analysis, the MAH displays data from VAERS, but not from EVDAS. Therefore, the assessor ran the query in EVDAS on 18 September 2024 with a receive date 13 February 2024. This showed a disproportionate reporting for the PT Migraine.

Active Substance (High Level) SARS-COV-2, SPIKE PROTEIN, RECOMBINANT, EXPRESSED IN SF9 CELLS DERIVED FROM SPODOPTERA FRUGIPERDA

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Migraine	[redacted]	4.24	5.78	41	2,027	55,514	11,639,539	11,697,121
Migraine with aura	0.29	2.05	14.59	1	2,067	2,755	11,692,298	11,697,121
Ophthalmic migraine	0.88	5.66	40.26	1	2,067	999	11,694,054	11,697,121
Typical aura without headache	7.66	54.93	393.88	1	2,067	103	11,694,950	11,697,121

Without restriction to the receive date, the query on 18 September 2024 with the MedDRA HLT Migraine headaches resulted in the following:

Active Substance (High Level) SARS-COV-2, SPIKE PROTEIN, RECOMBINANT, EXPRESSED IN SF9 CELLS DERIVED FROM SPODOPTERA FRUGIPERDA

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Migraine	[redacted]	4.32	5.86	42	2,052	56,974	12,023,707	12,082,775
Migraine with aura	0.29	2.03	14.45	1	2,093	2,838	12,077,843	12,082,775
Ophthalmic migraine	0.79	5.60	39.80	1	2,093	1,031	12,079,650	12,082,775
Typical aura without headache	7.60	54.45	390.34	1	2,093	106	12,080,575	12,082,775

The MAH does not discuss potential pathophysiological aspects in its signal evaluation report. All in all, however, the MAH's conclusion can be followed. An update of the product information or the RMP to include migraine events following vaccination with Nuvaxovid/Nuvaxovid XBB.1.5 is currently not considered warranted.

Signal evaluation report on tachycardia with use of Nuvaxovid/Nuvaxovid XBB.1.5

In PSUR Appendix 22 (pp. 792-885), the MAH provides its signal evaluation report for tachycardia, dated 03 May 2024. This report encompasses information available to the MAH from the clinical development integrated summary of safety and from the post authorisation setting. The reassessment of the safety signal of tachycardia had been requested by the FDA following the review of summary safety report (SSR) 26. Tachycardia is not included in the Nuvaxovid CCDS version 9.0 (effective 19 December 2023).

Methods

- Clinical trial data. The Nuvaxovid clinical safety analysis dataset (five completed and three ongoing clinical studies; 31,479 and 19,879 adult participants, respectively, in the NVX-CoV2373 and placebo groups) was searched for the MedDRA PTs Tachycardia, Heart rate increased, and Sinus tachycardia with a time to onset of 0-5 days post-vaccination.
- Post-authorisation data. A cumulative search of the post-authorisation safety database was performed with the MedDRA PTs Tachycardia, Heart rate increased, and Sinus tachycardia with a DLP of 22 March 2024. According to the FDA's request, ICSRs that were not clearly attributable to a specific physiologic trigger or diagnosis were included in the analysis. In addition, the MAH performed a broad

search using the standardised MedDRA queries (SMQs) *Arrhythmia related investigations, signs and symptoms* and *Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias)*.

- Disproportionality analysis. A VAERS data mining report was reviewed for the PTs Tachycardia, Heart rate increased, and Sinus tachycardia to assess whether any met the threshold for a signal of disproportionate reporting (EB05 > 2).

Results – Clinical trial data

The MAH states that in all periods – pre-crossover and post-crossover – events were infrequent and balanced between active and placebo groups with no meaningful risk differences

Table 13: Summary of tachycardia reported 5 days post any dose in adult population (overall safety analysis dataset; PSUR p. 806)

Pre-Crossover Period	Vaccine (n, %, 95% CI) N=30070	Placebo (n, %, 95% CI) N=19879	Risk Difference (Vaccine-Placebo) (%, 95% CI)
Any AE of Tachycardia	13 (0.04%), (0.02, 0.07)	5 (0.03%), (0.01, 0.06)	(0.02), (-0.01, 0.06)
Cardiac disorders	6 (0.02%), (0.01, 0.04)	5 (0.03%), (0.01, 0.06)	(-0.00) (-0.03, 0.02)
Tachycardia	4 (0.01%)	5 (0.03%)	(-0.01) (-0.03, 0.02)
Sinus tachycardia	2 (<0.01%)	0	(0.00) (-0.00, 0.01)
Investigations	7 (0.02%), (0.01, 0.05)	0 (0.00), (0.00, 0.02)	(0.03), (0.01, 0.05)
Heart rate increased	7 (0.02%)	0	(0.03), (0.01, 0.05)
Post-Crossover Period	**Vaccine (n, %, 95% CI) N=9634**	**Placebo (n, %, 95% CI) N=18584**	**Risk Difference (Vaccine-Placebo) (%, 95% CI)**
Any AE of Tachycardia	1 (0.01%), (0.00, 0.06)	4 (0.02%), (0.01, 0.06)	(-0.01), (-0.04, 0.02)
Cardiac disorders	1 (0.01%), (0.00, 0.06)	1 (<0.1%), (0.00, 0.03)	(0.01), (-0.02, 0.03)
Tachycardia	1 (0.01%)	1 (<0.01%)	(0.01), (-0.02, 0.03)
Investigations	0 (0.00), (0.00, 0.04)	3 (0.02%), (0.00, 0.05)	(-0.01), (0.03, 0.00)
Heart rate increased	0	3 (0.02%)	(-0.01), (0.03, 0.00)

Results – Post-authorisation safety data

Applying its narrow search strategy (PTs Tachycardia, Heart rate increased, and Sinus tachycardia), the MAH retrieved a total of 224 ICSRs without restriction regarding time to onset. Subsequent exclusions were made for those cases with time to onset falling outside the 0-5 day window (n = 73 cases) and following medical review for cases clearly attributable to a specific physiologic trigger or diagnosis (n = 45; thereof pyrexia, n = 22; hypersensitivity, n = 4; panic attack, n = 4; anxiety, n = 3; myocarditis/ pericarditis/ myopericarditis, n = 3). The remaining 106 ICSRs – 99 with Nuvaxovid and 7 with Nuvaxovid XBB.1.5 – concerned 87 females, 17 males and two persons of unknown gender.

Case characteristics of the focussed dataset (n = 106 cases) are summarised.

Table 14: Case characteristics of ICSRs retrieved for the MedDRA PTs Tachycardia, Heart rate increased, and Sinus tachycardia (excerpt from PSUR pp. 808-810)

		Novavax COVID-19 Vaccine, Adjuvanted (n=Number of ICSRs)	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) (n=Number of ICSRs)
Reports Retrieved		99	7
PTs retrieved by search strategy*	Tachycardia	80	4
	Heart rate increased	19	5
	Sinus tachycardia	2	0
Outcome (for PTs retrieved by the search strategy)	Not Recovered/Not Resolved	47	3
	Recovered/Resolved	22	4
	Recovering/Resolving	17	1
	Unknown	12	0
	Recovered with Sequelae	1	0
Time to Onset	0 days	43	3
	1 day	31	1
	2 days	8	0
	3 days	9	1
	4 days	5	1
	5 days	3	1

The most frequently co-reported PTs were Dizziness (n = 39), Headache (n = 31), Fatigue (n = 28), Dyspnoea (n = 22), Palpitations (n = 22), and Nausea (n = 21).

Case series are presented in Table 7 (no distinct physiological trigger or diagnosis for the reported events of tachycardia; n = 52;causality noted by the MAH as *consistent with causal association with vaccine based on temporal relationship and lack of confounders and/or alternative aetiology*) and Table 8 (cases include co-reported events that may have contributed to the development of tachycardia or are suggestive of an alternative aetiology; n = 54; causality noted by the MAH as *inconsistent causal association with vaccine based on information regarding medical history and/or concurrent events that support a reasonable alternative aetiology* or as *indeterminate causal association with vaccine based on the limited information provided and/or medical history or concurrent events that may have contributed to the development of the reported event*) of the signal evaluation report.

Using the broad search strategy, the MAH retrieved a total of 518 ICSRs for Nuvaxovid and 26 ICSRs for Nuvaxovid XBB.1.5. The MAH did not identify apparent patterns or trends that would suggest specific diagnoses. It points out that cases are confounded by concurrent events, some of which may relate to listed events including hypersensitivity or vaccination anxiety-related events or other topics under review such as myocarditis/pericarditis.

Table 15: Case characteristics of ICSRs retrieved for the MedDRA SMQs Arrhythmia related investigations, signs and symptoms and Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) (excerpt from PSUR pp. 878-882)

		Novavax COVID-19 Vaccine, Adjuvanted (n=number of ICSRs)	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) (n=number of ICSRs)
Reports Retrieved		518	26
Outcome (for PTs retrieved by the search strategy)	Not Recovered/Not Resolved	216	9
	Recovered/Resolved	121	8
	Unknown	110	7
	Recovering/Resolving	87	4
	Recovered with Sequelae	11	0
	Fatal	2	1
Time to onset	0-5	293	15
	6-10	24	1
	11-20	20	0
	21+	24	2
	UNK	176	10

The most frequently reported PTs retrieved by the search strategy were Palpitations (n = 217), Tachycardia (n = 166), Heart rate increased (n = 64), Arrhythmia (n = 53), Syncope (n = 48), and Loss of consciousness (n = 25). The PT Electrocardiogram abnormal was coded in 14 cases. The most frequently co-reported PTs were Headache (n = 148), Fatigue (n = 134), Dizziness (n = 127), Chest pain (n = 120), Dyspnoea (n = 120), and Nausea (n = 94).

Results – Disproportionality analysis

As of 23 February 2024, results for the PT Heart rate increased met a threshold for signal of disproportionate reporting (EB05 = 2.02; cumulative count, n = 18), while Tachycardia (EB05 = 0.654; cumulative count, n = 10) and Sinus Tachycardia (EB05 = 0.211; cumulative count, n = 1) did not.

Conclusion

The MAH concludes that its comprehensive review did not identify any evidence of a causal association between Nuvaxovid and tachycardia beyond temporal association.

Rapporteur assessment comment:

A reassessment of the safety signal of tachycardia had been requested by the US FDA in March 2024, including the search strategies applied (MedDRA SMQs, MedDRA PTs and exclusion of cases). The MAH performed the analysis as requested by the FDA; therefore, the narrow search did not include, for example, the MedDRA PTs Atrial tachycardia and Ventricular tachycardia.

Across five completed and three ongoing clinical trials in adults, events were overall infrequent and balanced between active and placebo groups.

Of a total of 224 ICSRs in the global safety database, 118 were excluded from the focussed review in line with FDA requirements (event latency > 5 days, n = 73; cases clearly attributable to a specific physiologic trigger or diagnosis, n = 45). For 52 cases presented in Table 7 (PSUR pp. 811-837), the MAH categorised causality as *consistent with causal association with vaccine based on temporal relationship and lack of confounders and/or alternative aetiology*. For 20 cases, the MAH noted an *inconsistent causal association with vaccine based on information regarding medical history and/or concurrent events that support a reasonable alternative aetiology*, and for 34 cases an *indeterminate causal association with vaccine based on the limited information provided and/or medical history or concurrent events that may*

have contributed to the development of the reported event (Table 8, PSUR pp. 838-877). For the assessor, the causality categorisation made by the MAH is not always comprehensible. However, it is noted that events coded under the MedDRA PTs Tachycardia, Heart rate increased, and Sinus tachycardia PTs were reported in a close temporal context with the vaccination (time to onset 0 days in n = 46 cases). The current product information for Nuvaxovid and Nuvaxovid XBB.1.5 does not refer to tachycardia, although it does list reactions that may be associated with tachycardia, such as pyrexia and (injection site) pain (SmPC section 4.8) or anxiety-related reactions (SmPC section 4.4).

As regards disproportionality analysis, the MAH displays data from VAERS, but not from EVDAS. Therefore, the assessor ran the query in EVDAS on 23 September 2024 with the following results.

Active Substance (High Level): SARS-COV-2, SPIKE PROTEIN, RECOMBINANT, EXPRESSED IN SF9 CELLS DERIVED FROM SPODOPTERA FRUGIPERDA

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Heart rate increased	1.86	2.66	3.82	30	2,241	60,509	12,028,096	12,090,876
Sinus tachycardia	0.57	1.77	5.49	3	2,268	9,033	12,079,572	12,090,876
Tachycardia	5.02	6.68	7.94	138	2,133	115,965	11,972,640	12,090,876

Active Substance (High Level): MATRIX M, SARS-COV-2, VARIANT OMICRON XBB.1.5, SPIKE PROTEIN, RECOMBINANT, EXPRESSED IN SF9 CELLS DERIVED FROM SPODOPTERA

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Heart rate increased	0.32	2.28	16.40	1	87	60,538	12,030,250	12,090,876
Tachycardia	2.52	6.21	15.32	5	83	116,098	11,974,690	12,090,876

It is noted that these three MedDRA PTs are also reported for mRNA vaccines against COVID-19. Here, tachycardia is not listed as an adverse reaction in SmPC section 4.8, but is mentioned in the context of anxiety-related reactions with tozinameran (SmPC section 4.4, "increases in heart rate").

Active Substance (High Level): TOZINAMERAN

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Heart rate increased	1.65	1.69	1.73	9,954	1,254,211	50,585	10,776,126	12,090,876
Sinus tachycardia	0.71	0.77	0.83	743	1,263,422	8,293	10,818,418	12,090,876
Tachycardia	2.30	2.33	2.36	24,597	1,239,568	91,506	10,735,205	12,090,876

Active Substance (High Level): ELASOMERAN

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A + B + C + D]
Heart rate increased	1.61	1.67	1.73	3,166	384,319	57,373	11,646,018	12,090,876
Sinus tachycardia	0.67	0.76	0.87	222	387,263	8,814	11,694,577	12,090,876
Tachycardia	1.99	2.04	2.09	7,277	380,208	108,826	11,594,565	12,090,876

A discussion of the literature or pathophysiology by the MAH would have been considered valuable. All in all, in view of the data presented, it is agreed with the MAH that the available evidence does not suggest specific conditions which are caused by the vaccine and characterised by tachycardia. In particular, there was no imbalance between vaccine and placebo in the clinical trials with Nuvaxovid. An update of the product information or the RMP to include tachycardia following vaccination with Nuvaxovid/Nuvaxovid XBB.1.5 is currently not considered warranted.

Addendum to the signal evaluation report on tachycardia with use of Nuvaxovid/Nuvaxovid XBB.1.5

In PSUR Appendix 23 (pp. 886-891), the MAH provides an addendum to the signal evaluation report for tinnitus, dated 28 March 2024. It summarises the course of this safety signal, starting with the PRAC procedure EMEA/H/C/PSUSA/00010972/202206, and concludes that, in response to US FDA and EMA population-based assessments and known limitations of post-authorisation data, it is in agreement to update the final disposition of the signal tinnitus to status *refuted*. Tinnitus will be removed from the Nuvaxovid CCDS and will remain in the post authorisation section of the Australian product information

(section 4.8). The MAH states that events of tinnitus will continue to be monitored under routine pharmacovigilance including information regarding plausible mechanisms.

Rapporteur assessment comment:

It is agreed with the MAH that determining the sufficiency of evidence supporting a causal association between vaccine administration and an adverse event is complex, requires judgement and may evolve over time. The MAH's intention to continue monitoring events of tinnitus under routine pharmacovigilance is endorsed.

2.3. Evaluation of risks and safety topics under monitoring

The MAH monitors the following **adverse events of special interest** (AESIs): Acute disseminated encephalomyelitis, anaphylaxis, autoimmune hepatitis, autoimmune thyroiditis, Bell's palsy, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis and encephalomyelitis, fibromyalgia, foetal growth restriction, generalised convulsions, gestational diabetes, Guillain-Barré syndrome, haemorrhagic stroke, ischaemic stroke, Kawasaki's disease, major congenital anomalies, maternal death, microcephaly, multiple sclerosis, multisystem inflammatory syndrome in children, myasthenia gravis, myocardial infarction, myocarditis, myocarditis and pericarditis, pericarditis, narcolepsy, neonatal death, oculomotor cranial nerve disorders, optic neuritis, postural orthostatic tachycardia syndrome, preeclampsia, preterm birth, rheumatoid arthritis, spontaneous abortion, stillbirth, sudden death, thrombocytopenia, thrombosis with thrombocytopenia syndrome, transverse myelitis, vaccine-associated enhanced disease, and venous thromboembolism.

For a presentation of the methods and results, it is referred to the PSUR (section 15.2, pp. 78-130) and its appendices (Appendix 11, O/E analyses and exposure data assumptions, pp. 475-508; Appendix 12, O/E analyses, pp. 509-654; Appendix 13, search strategy/methodology for AESI, pp. 655-656). The MAH notes that O/E calculations are not performed for vaccine associated enhanced disease or pregnancy-related AESIs due to data limitations impacting numerators and/or denominators. Results are provided for both vaccines combined (Novavax COVID-19 vaccines), as well as for Nuvaxovid and Nuvaxovid XBB.1.5.

Cumulatively up to the DLP of 19 June 2024, no ICSRs were retrieved for the following 10 AESIs for any Nuvaxovid formulation: Acute disseminated encephalomyelitis, foetal growth restriction, gestational diabetes, Kawasaki's disease, major congenital anomalies, maternal death, microcephaly, narcolepsy, neonatal death, and stillbirth. In addition, for Nuvaxovid XBB.1.5, no ICSRs were retrieved either cumulatively or for the reporting interval for the following 16 AESIs: Anaphylaxis, autoimmune hepatitis, autoimmune thyroiditis, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis and encephalomyelitis, Guillain-Barré syndrome, haemorrhagic stroke, multiple sclerosis, multisystem inflammatory syndrome in children, myasthenia gravis, myocardial infarction, optic neuritis, thrombocytopenia, thrombosis with thrombocytopenia syndrome, and vaccine-associated enhanced disease.

During the reporting interval, no new AESI signals were validated. On sensitivity analysis for the AESI of generalised convulsions with the assumption of 75% underreporting at the 0-1 day risk window, the all-formulation observed rate was significantly greater than expected (RR = 2.13; 95% CI: 1.02-3.92). When assessing by vaccine formulation, results for Nuvaxovid and Nuvaxovid XBB.1.5 remained greater than expected, but these results were not statistically significant. For the AESIs of myocarditis and myocarditis/pericarditis (0-7 day risk window), the all-formulation results for myocarditis (RR = 10.42; 95% CI: 6.80-15.26) and myocarditis/pericarditis (RR = 4.25; 95% CI: 3.34-5.32) were statistically significant. Of the 5 ICSRs incorporated into the Nuvaxovid XBB.1.5 O/E analyses, no cases met Brighton Collaboration case definitions levels 1-3 for either myocarditis or pericarditis. The MAH did not detect any significant changes in O/E for the remaining AESIs.

Table 16: Number of ICSRs retrieved for AESIs monitored by the MAH and for which cases have been reported (PSUR section 15.2, pp. 78-130)

Number of ICSRs	**Nuvaxovid**		**Nuvaxovid XBB.1.5**	
	Interval	Cumulatively	Interval	Cumulatively
Anaphylaxis	3	74	0	0
Autoimmune hepatitis	0	2	0	0
Autoimmune thyroiditis	0	3	0	0
Bell's palsy	0	24	2	2
Cerebral venous sinus thrombosis	0	1	0	0
Chronic fatigue syndrome	0	3	0	0
Encephalitis and encephalomyelitis	3	5	0	0
Fibromyalgia	1	4	0	1
Generalised convulsions	0	13	1	2
Guillain-Barré syndrome	2	10	0	0
Haemorrhagic stroke	0	11	0	0
Ischaemic stroke	0	17	2	2
Multiple sclerosis	0	3	0	0
Multisystem inflammatory syndrome in children	0	1 (adult case)	0	0
Myasthenia gravis	0	1	0	0
Myocardial infarction	1	16	0	0
Myocarditis	2	31	2	2
Pericarditis	3	57	2	3
Myocarditis and pericarditis	4	89	5	6
Oculomotor cranial nerve disorders	0	0	1	1
Optic neuritis	0	1	0	0
Postural orthostatic tachycardia syndrome	2	5	1	1
Preeclampsia	0	2	1	1
Preterm birth	0	2 (linked – maternal and neonate)	2	2 (linked – maternal and neonate)
Rheumatoid arthritis	2	8	1	1
Spontaneous abortion	0	4	1	1
Sudden death	1	1	1	1
Thrombocytopenia	1	9	0	0
Thrombosis with thrombocytopenia syndrome	0	1	0	0
Transverse myelitis	1	1	0	1
Vaccine associated enhanced disease	0	7	0	0
Venous thromboembolism	1	23	1	2

Further, the MAH queried its global vaccine safety database for the following **additional safety topics for monitoring** up to 19 June 2024: Death (all cause), cholecystitis, diarrhoea, herpes zoster, inflammatory eye disorders, menstrual disorders, paraesthesia, reactogenicity profile – second dose and

boosters (based on impurity levels), safety concerns in elderly and off-label paediatric use, tinnitus, vaccine anxiety-related reactions, and vaccination failures/lack of efficacy.

As regards its review of safety concerns in elderly, the MAH notes that it reviewed the disproportionate reporting of expired product administered in PSUR section 9.2 and that all other reports were consistent with the general AE profile as defined in the CCDS for the overall population.

Table 17: Number of ICSRs retrieved for additional safety topics monitored by the MAH (PSUR section 15.3, pp. 131-141)

Number of ICSRs	**Nuvaxovid**		**Nuvaxovid XBB.1.5**	
	Interval	Cumulatively	Interval	Cumulatively
Death, all cause	3	34	8	8
Cholecystitis	1	9	1	1
Diarrhoea	6	137	4	7
Herpes zoster	0	40	1	1
Inflammatory eye disorders	2	66	1	4
Menstrual disorders	3	138	0	0
Paraesthesia	14	415	9	19
Reactogenicity profile – second dose and boosters (based on impurity levels)	29	317	8	9
Safety concerns in elderly	29	729	65	97
Off-label paediatric use (< 12 years)	0	12	1	3
Tinnitus	1	87	6	9
Vaccine anxiety-related reactions	3	58	3	4
Vaccination failures*/lack of efficacy	5	22	4	6

*The MAH defines vaccination failure as meeting three criteria – (i) associated Covid-19 symptoms are reported; (ii) the reported events occur 7 or more days past the date of the second vaccination, or booster administration; (iii) a positive diagnostic test for COVID-19 is also reported in the case.

Rapporteur assessment comment:

The MAH monitors 42 AESIs which, however, cover only some of the AEs relevant to COVID-19 vaccine trials and listed by the Brighton Collaboration (https://brightoncollaboration.org/covid-19-aesi-list-5th-update-october-2022/). In its response to the requests arising from procedure EMEA/H/C/PSUSA/00010972/202312, the MAH states that it incorporated *acute kidney injury* and *acute liver injury* to the list of prospectively monitored AESIs and that results will be reported beginning with the 6th PSUR. The MAH points out that other AESIs on the Brighton Collaboration list that are not separately included in its AESI list fall under one of three categories of on-going, prospective surveillance with validated signals summarised in PSURs. This is noted.

As in previous PSURs, there is an increased O/E ratio for events of anaphylaxis, myocarditis and pericarditis – events that have been included in the product information. The MAH's analysis of cases reporting generalised convulsions showed that, for the risk window of 0-1 days, the unadjudicated observed count was significantly greater than expected at 75% sensitivity for all formulations, but not when stratified by vaccine. For Guillain-Barré syndrome and Nuvaxovid, the unadjudicated observed rate was significantly increased compared to the expected rate when assuming 75% underreporting.

Also in the presentation of the AESIs, it is noted that fewer ICSRs were reported for Nuvaxovid XBB.1.5, even taking into account the lower exposure. The reasons for this could be discussed, but the variant-adapted vaccine alone is unlikely to explain these findings. Instead, differences in the vaccinated

population, immunisation recommendations and a change in reporting behaviour might be considered.

The MAH states that during the reporting interval, it expanded its search strategy for inflammatory eye disorders to include selected PTs. However, the search strategy described in Appendix 14 of the current PSUR, including the specified PTs, is unchanged from the strategy specified in the last PSUR, procedure EMEA/H/C/PSUSA/00010972/202312. It is therefore unclear as to how the MAH's search was modified.

Taking into consideration the MAH's review of the risks, no further action is considered warranted at this stage.

2.4. Characterisation of risks

New information on important identified risks

Myocarditis and/or pericarditis

Nuvaxovid: For the reporting interval, the MAH retrieved 5 initial and 3 follow-up ICSRs. Of a cumulative total of 136 ICSRs, 52 met level 1-3 Brighton Collaboration case definitions for myocarditis and/or pericarditis. In these 52 cases, the most frequent co-reported PTs (PSUR Table 30, p. 148) were Chest pain (n = 27), Pericarditis (n = 18), Dyspnoea (n = 15), Palpitations (n = 10), and Myocarditis (n = 10). In 26 cases (50.0%), time to onset was 0-7 days.

Nuvaxovid XBB.1.5: For the reporting interval, the MAH retrieved 11 initial and 1 follow-up ICSRs. Of a cumulative total of 15 ICSRs, none met level 1-3 Brighton Collaboration case definitions for myocarditis and/or pericarditis.

Data from South Korea, published by the Korean Disease Control and Prevention Agency (KDCA), reported a total of 5 confirmed cases of myocarditis with Nuvaxovid (adjudicated against a modified algorithm based on the Brighton Collaboration case definition). Four of the 5 confirmed cases have been received as ICSRs in the company safety database and are considered as level 1-3 (exact level unknown). No cases were reported with Nuvaxovid XBB.1.5.

The MAH concludes that no significant safety information was received on the risk of myocarditis and/or pericarditis during the reporting interval that would alter its already established characterisation.

New information on important potential risks

Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease

Nuvaxovid: The MAH retrieved no ICSR for the reporting interval and 7 ICSRs cumulatively, which were all coded to the PT *Antibody-dependent enhancement*.

Nuvaxovid XBB.1.5: The MAH did not retrieve any ICSR.

Update on missing information

Use in pregnancy and while breastfeeding

Nuvaxovid: As regards use in pregnancy, the MAH retrieved no ICSR for the reporting interval and 14 ICSRs cumulatively. Nuvaxovid XBB.1.5: As regards use in pregnancy, the MAH retrieved 3 initial and 6 follow-up ICSRs for the reporting interval, and a cumulative total of 16 ICSRs.

The MAH states that an analysis could not be performed as gestational age, obstetric details, medical history, concomitant medication, and further details were unknown. It concludes that none of the reports of use in pregnancy raises any safety concerns.

Nuvaxovid: No foetal and neonate ICSR was retrieved for the reporting interval, and 4 ICSRs were retrieved cumulatively involving 1 foetus and 3 neonates. Nuvaxovid XBB.1.5: One initial and 1 follow-up foetal/neonate ICSRs were retrieved for the reporting interval, and 3 ICSRs were retrieved cumulatively involving 2 foeti and 1 neonate. The MAH did not identify any safety signal.

Nuvaxovid: Concerning use while breastfeeding, no ICSRs were retrieved for the reporting interval, and 3 ICSRs were retrieved cumulatively. Nuvaxovid XBB.1.5: No ICSRs were retrieved either cumulatively or for the reporting interval.

According to the MAH, none of the reports of use during pregnancy and breastfeeding raised any safety concerns.

Use in immunocompromised patients

The MAH states that an increase in ICSRs, above what is expected by typical patterns of reporting, was retrieved for its search in the global vaccine safety database relative to the prior PSUR. It did not detect any notable differences or trends across the general and immunocompromised populations on review of new ICSR inclusions to the dataset.

Nuvaxovid: The MAH retrieved 6 initial ICSRs for the reporting interval and 29 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved 4 initial and 2 follow-up ICSRs for the reporting interval and 6 ICSRs cumulatively.

The MAH's review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)

Nuvaxovid: The MAH retrieved 25 initial and 18 follow-up ICSRs for the reporting interval and 645 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved 76 initial and 14 follow-up ICSRs for the reporting interval and 131 ICSRs cumulatively. The MAH's review of the reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Use in patients with autoimmune or inflammatory disorders

Nuvaxovid: The MAH retrieved 11 initial and 6 follow-up ICSRs for the reporting interval and 211 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved 31 initial and 3 follow-up ICSRs for the reporting interval and 54 ICSRs cumulatively. The MAH's review of the reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Interaction with other vaccines

Nuvaxovid: No ICSR was retrieved for the reporting interval, and two ICSRs were retrieved cumulatively. After assessment, the MAH concluded that both reports did not meet the inclusion criteria. Nuvaxovid XBB.1.5: The MAH retrieved no ICSR. The MAH did not identify any new information determining interaction with other vaccines.

Long-term safety

The MAH notes that long-term safety is evaluated by routine monitoring of PASSs. There were three ongoing PASSs during the reporting interval and no clinically significant safety findings were reported from any of those studies.

Rapporteur assessment comment:

The safety concerns remain unchanged.

3. Benefit evaluation

Efficacy and immunogenicity of Nuvaxovid in adolescent participants 12 to < 18 years of age were assessed in the ongoing paediatric expansion portion of study 2019nCoV-301 (US). A total of 1,799 participants assigned in a 2:1 ratio to receive two doses of Nuvaxovid (n = 1,205) or placebo (n = 594) represented the primary efficacy population. There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (Nuvaxovid, n = 6; placebo, n = 14) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8, 92.1). The safety and immunogenicity of a Nuvaxovid booster dose was evaluated in 220 adolescents.

In the adult main study 2019nCoV-301, the primary efficacy analysis population included 25,452 participants who received two doses of either Nuvaxovid (n = 17,312) or placebo (n = 8,140). Vaccine efficacy to prevent the onset of COVID-19 from 7 days after dose 2 was 90.4% (95% CI: 82.9, 94.6). No cases of severe COVID-19 were reported in the Nuvaxovid participants compared with 4 cases of severe COVID-19 reported in the placebo recipients.

In study 2019nCoV-302, a total of 7,020 and 7,019 adult participants received two doses of Nuvaxovid and placebo, respectively. Efficacy of Nuvaxovid to prevent the onset of COVID-19 from 7 days after dose 2 was 89.7% (95% CI: 80.2, 94.6). No cases of severe COVID-19 were reported in the Nuvaxovid participants compared with 5/4 cases of severe COVID-19 reported in the placebo recipients.

The safety and immunogenicity of a booster dose of either the original monovalent Nuvaxovid (NVX-CoV2373), the monovalent vaccine Omicron BA.1 (NVX-CoV2515), the monovalent vaccine Omicron BA.5 (NVXCoV2540), or a bivalent study vaccine (+NVX-CoV2515 or + NVX-CoV2540), was evaluated in study 2019nCoV-311. The analysis of the geometric mean titre (GMT) ratio following the booster dose with the monovalent vaccine (Omicron BA.1) compared to the booster dose with the original monovalent vaccine met the superiority criterion for success (lower limit of the 95% CI > 1.0).

Rapporteur assessment comment:

There are no new data on efficacy that alters previous assessments, and which are described in the approved product information. The MAH's summary of new information from the literature (9 publications) is appreciated.

Note: When presenting the results of study 2019nCoV-302, the MAH gives inconsistent numbers of severe COVID-19 cases in placebo recipients (5 versus 4, PSUR p. 162). The marketing authorisation for Jcovden was withdrawn in the EU on 26 July 2024 (withdrawal adopted by the European Commission; effective withdrawal date 09 August 2024) after the DLP for this PSUR.

4. Benefit-risk balance

The data presented does not include significant new information that alters previous assessments of efficacy or safety. The PRAC rapporteur therefore concludes that the benefit-risk balance for Nuvaxovid

and Nuvaxovid XBB.1.5 remains unchanged in its authorised indications. The MAH's commitment to continue monitoring safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines is acknowledged.

5. Rapporteur request for supplementary information

1) PSUR section 5.2 *Cumulative and interval exposure in the post-authorisation setting*: The MAH's statement on distributed doses is not comprehensible – if no Nuvaxovid doses were distributed during the reporting interval, the cumulative number of distributed doses should not differ between this (n = 124,790,110) and the previous PSUR (n = 115,971,670). The MAH is kindly asked to clarify this discrepancy.

6. MAH response to request for supplementary information

The MAH acknowledges the discrepancy between the numbers presented in the 4th PSUR (n = 115,971,670) and the 5th PSUR (n = 124,790,110). In PSURs prior to PSUR 5, the distributed doses presented were adjusted for doses returned under specific purchasing agreements. However, this adjustment to the distributed doses was discontinued as of PSUR 5, with totals again reflecting all distributed doses. This led to a one-time addition of the returned doses back into total counts and the perceived discrepancy between interval and cumulative distributions.

Rapporteur assessment comment:

According to the MAH, the higher cumulative number of distributed doses in this reporting interval can be explained by returned doses that were considered in previous PSURs but not in the current PSUR. In the current PSUR, the cumulative number of distributed doses includes both returned and non-returned doses.

Issue considered resolved. However, if the number of returned doses is known, it might be appropriate to (negatively) reflect this in the total number of distributed doses.

7. Comments from Member States

No comments were received from member states.

PERIODIC BENEFIT-RISK EVALUATION REPORT

FOR

PRODUCT: NUVAXOVID/NUVAXOVID XBB.1.5 DISPERSION FOR INJECTION COVID-19 VACCINE (RECOMBINANT, ADJUVANTED)

ATC CODE: [J07BN04]

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Products	Marketing Authorisation Number(s)	Dates of Authorisation	Marketing Authorisation Holder
NUVAXOVID™	EU/1/21/1618/001 EU/1/21/1618/002 EU/1/21/1618/003 EU/1/21/1618/004	20-Dec-2021	Novavax CZ a.s
NUVAXOVID XBB.1.5	EU/1/21/1618/006 EU/1/21/1618/008	31-Oct-2023	Novavax CZ a.s

AUTHORISATION PROCEDURE in the EU: Marketing Authorisation

INTERNATIONAL BIRTH DATE (IBD): 20-Dec-2021

EUROPEAN UNION REFERENCE DATE (EURD): 20-Dec-2021

INTERVAL COVERED BY THIS REPORT: 20-Dec-2023 to 19-Jun-2024

Date of Report: 15-Aug-2024

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

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NAME AND CONTACT DETAILS OF THE QPPV:

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Electronic signature approval(s) signifies that the approver approves this document as acceptable, accurate, and complete.

DESCRIPTION	NAME / TITLE	SIGNATURE / DATE
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APPROVED BY:	[redacted] Global Vaccine Safety	

EXECUTIVE SUMMARY

Introduction

This is the fifth Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™, summarising interval and cumulative safety data received by Novavax (NVX) for the reporting interval 20-Dec-2023 to 19-Jun-2024. This PBRER also includes exposure and safety data for Nuvaxovid™ XBB.1.5, which is Nuvaxovid updated for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron XBB.1.5 sub-variant. As used in this report, the term "original vaccine" refers to Nuvaxovid, the term "updated vaccine" refers to Nuvaxovid XBB.1.5, and the term "Novavax COVID-19 vaccines" refers to both Nuvaxovid and Nuvaxovid XBB.1.5 (i.e., both the original and updated vaccines).

The format and content of this PBRER complies with: the Guideline on GVP Module VII-Periodic safety update report (EMA/816292/2011 [Dec-2013]), the ICH Guideline E2C (R2) Periodic Benefit-Risk Evaluation Report [Step 5, Jan-2013]), the core PSUR19 guidance (EMA/362988/2021 [08-Jul-2021]), and the Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance V. 3.1 (EMA/PRAC/709308/2022 [01-Sep-2022]). The periodicity of this PBRER is based on the European Union (EU) birth date (international birth date) of 20-Dec-2021, for Nuvaxovid.

NVX has developed recombinant Spike (rS) protein nanoparticle vaccines for active immunisation to prevent COVID-19 caused by SARS-CoV-2 and variants of concern. All SARS-CoV-2 rS nanoparticle vaccines contain purified recombinant Spike (rS) protein antigens stabilized in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against COVID-19.

NVX developed five monovalent nanoparticle study vaccines (NVX-CoV2373, NVX-CoV2515, NVX-CoV2540, NVX-CoV2601 and NVX-CoV2705) containing components of original SARS-CoV-2 Wuhan strain, or variants, Omicron BA.1, Omicron BA.5, Omicron XBB.1.5, or JN.1, respectively. Currently two of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373) and Nuvaxovid XBB.1.5 (NVX-CoV2601). In this report, the trade names, Nuvaxovid and Nuvaxovid XBB.1.5, are used when referring to these vaccines in the post-authorisation/post-marketing setting, while Novavax's study vaccine names, NVX-CoV2373 (or Prototype) and NVX-CoV2601, are used when referring to these vaccines in clinical trials. The table below describes the properties of Nuvaxovid and Nuvaxovid XBB.1.5.

Parameters	Nuvaxovid	Nuvaxovid XBB.1.5
Vaccine code	NVX-CoV2373	NVX-CoV2601
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5
Description	Colourless to slightly yellow and clear to mildly opalescent dispersion for injection.	
Composition	One dose (0.5 mL) contains 5 micrograms of recombinant SARS-CoV-2 Spike protein produced by the recombinant DNA technology using a Baculovirus protein expression system (in an insect cell line derived from Sf9 cells of the *Spodoptera frugiperda* species) and 50 µg of the saponin-based adjuvant Matrix-M™ which contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of *Quillaja saponaria* Molina extract.	
Dosage Forms	Multi-dose vial containing either 5 or 10 doses per vial	Multi-dose vial containing 5 doses per vial
Indication	Active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.	
Dosage	Primary vaccination series: Administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended to administer the second Dose 3 weeks after the first dose. Booster dose: Administered intramuscularly approximately 3 months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose) Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an mRNA vaccine or adenoviral vector vaccine (heterologous booster dose).	Administered intramuscularly as a single Dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine in individuals who have previously been vaccinated. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

Worldwide Marketing Authorisation Status

Nuvaxovid:

Nuvaxovid has received marketing authorisation or emergency use authorisation as a two-dose primary series and as a booster for individuals 12 years and older, in multiple countries, the EU region and by the World Health Organisation (WHO), an agency of the United Nations, under the trade names, Nuvaxovid™, Covovax™, and Novavax COVID-19 Vaccine, Adjuvanted in the United States (US). In India, Covovax is authorised as a two-dose primary series in individuals 7 years of age and older and as a booster for individuals 18 years of age and older. In Japan, Nuvaxovid is authorised as a two-dose primary series in individuals 6 years of age and older, and as a booster in individuals 12 years of age and older.

During the reporting interval:

- Covovax received marketing authorisation in Brazil as a primary series for individuals 12 years and older.
- Nuvaxovid received marketing authorisation in Japan as a primary series for individuals aged 6 years and older.

Nuvaxovid XBB.1.5:

Nuvaxovid XBB.1.5 received authorization for emergency use, or received marketing authorization, for individuals 12 years and older in multiple countries, the EU region and by the WHO, under the trade names Nuvaxovid XBB.1.5, Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula) in Brazil, Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in the US and Novavax COVID-19 Vaccine 2023-2024 formula in South Korea.

During the reporting interval:

- Nuvaxovid XBB.1.5 received marketing authorisation in United Kingdom (UK).
- Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula) received approval in Brazil.
- Nuvaxovid XBB.1.5 received approval in Singapore.

Actions Taken for Safety Reasons

None.

Changes to Reference Safety Information

Company Core Data Sheet (CCDS) Version (v) 9.0, dated 19-Dec-2023 was in effect at the beginning of the reporting interval. During the reporting interval, CCDS v9.0 was updated to v10.0 (effective date 30-May-2024) to remove tinnitus from the adverse reactions from post-marketing experience in Section 4.8.2 and to add information on the JN.1/2024-2025 Formula and prefilled syringe presentation.

Clinical Trial Exposure

Cumulatively, 48,380 participants have been exposed to at least one dose of SARS-CoV-2 rS vaccines (either monovalent or bivalent, prototype or variant), in the Novavax clinical development program. A total of 5,075 participants are engaged in blinded treatment arms of studies across the NVX sponsored SARS-CoV-2rS clinical development program. An additional 1,422 participants were exposed to the COVID-19 influenza combination (CIC) vaccine in 2 NVX sponsored clinical trials involving CIC vaccine.

Post-Authorisation Exposure

Exposure to Nuvaxovid:

During the reporting interval, no doses of Nuvaxovid were distributed and 5,797 Nuvaxovid doses were administered (4,219 Nuvaxovid doses in Australia, Canada, and Japan and 1,578 Covovax doses in India).

Cumulatively, 124,790,110 Nuvaxovid doses (115,455,860 Nuvaxovid and 9,334,250 Covovax doses) were distributed and 2,989,177 Nuvaxovid doses were administered (2,934,244 Nuvaxovid doses administered in Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, UK, and US and 54,933 Covovax doses administered in India).

Exposure to Nuvaxovid XBB.1.5:

During the reporting interval, 9,009,590 Nuvaxovid XBB.1.5 doses were distributed and 1,048,691 Nuvaxovid XBB.1.5. doses were reported to have been administered in Canada, EU, South Korea, Taiwan and US.

Cumulatively, 18,101,000 Nuvaxovid XBB.1.5 doses were distributed and 1,201,601 Nuvaxovid XBB.1.5 doses were administered (Canada, EU, South Korea, Taiwan and US). As of the data lock point (DLP) of this report, administration information from other countries/regions was not yet available.

Overview of Signals: New, Ongoing, or Closed

No new signals were generated for Adverse Events of Special Interest (AESI) through Observed-to-Expected (O/E) analyses during the reporting interval. Migraine and tachycardia became validated signals during the reporting interval following health authority requests from Therapeutic Goods Administration and US Food and Drug Administration (FDA), respectively. Both signals were refuted upon evaluation.

The final disposition of a previously validated signal of tinnitus was updated to refuted during the reporting interval in response to US FDA and European Medicines Agency assessments. Tinnitus has been removed from the adverse reactions from post-marketing experience section (Section 4.8) of the CCDS v10.0, effective 30-May-2024 and will remain in the post authorisation section of the Australian Product Information (Section 4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance.

The signals of anaphylaxis, paraesthesia, myopericarditis, myocarditis and pericarditis have been previously confirmed and the CCDS was updated accordingly.

Validated signals previously evaluated, refuted and closed include acute coronary syndrome associated with hypersensitivity, chest pain/chest discomfort, diarrhoea, dizziness, dyspnoea,

encephalitis/encephalomyelitis, menstrual disorders, oculomotor cranial nerve disorders, syncope, sensorineural hearing loss, tachycardia and other rhythm disorders.

Confirmed and refuted signals will continue to be monitored according to routine surveillance.

Summary Evaluation of Important Risks and New Information

No new important risks and no new information related to existing risks have been identified in the reporting interval.

Overall Benefit-Risk Evaluation

Based on the totality of the data across the SARS-CoV-2 rS clinical development program, the Novavax COVID-19 vaccines administered as either 2 intramuscular injections at least 21 days (+ 7 days) apart as primary series vaccination or as 1 intramuscular injection in previously vaccinated individuals is an effective vaccine with an acceptable safety profile for the active immunisation for the prevention of COVID-19 caused by SARS-CoV-2 in both adults ≥ 18 years of age and adolescents 12 to < 18 years of age. Homologous booster vaccination in adult and adolescent participants induced robust immune responses that exceeded those reported following primary series vaccination. Heterologous booster vaccination in adult participants also resulted in robust increases in neutralising antibody titers. The dose of the Novavax COVID-19 vaccines for both primary and booster injections is the same for all ages, thus facilitating ease of use for vaccine administrators and reducing the likelihood of dosing errors.

Considering the endemicity of SARS-CoV-2, emergence of new antigenic variants, and the need for additional effective vaccine options, along with the available efficacy/effectiveness, immunogenicity, and safety data across the SARS-CoV-2 rS clinical development program, NVX considers that the known and potential benefits outweigh the known and potential risks of the Novavax COVID-19 vaccines and support authorisation for individuals ≥ 12 years of age for primary series vaccination and for periodic revaccination.

Conclusion

Across the clinical development and post-authorisation lifecycle up to 19-Jun-2024 and in conjunction with current Nuvaxovid reference safety information, the benefit-risk balance of Novavax COVID-19 Vaccines remains positive.

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LIST OF ABBREVIATIONS

Acronym	Abbreviation Definition
µg	Micrograms
ACCESS	The vACCine COVID-19 monitoring readinESS Project
ADCC	Antibody-dependent Cytotoxicity
ADCD	Antibody-dependent Complement Deposition
ADCP	antibody-dependent Cellular Phagocytosis
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AEFI(s)	Adverse Events Following Immunisation(s)
AESI(s)	Adverse Event(s) of Special Interest
AZD1222	Oxford-AstraZeneca Adenovirus-based
BALB/c	Albino, Laboratory-Bred Strain of the house Mouse, MHC Haplotype H2d
BEST	Biologics Effectiveness and Safety
BLA	Biologics License Application
BNT	BNT162b2 Pfizer–BioNTech
BODIPY	Boron-Dipyrromethane
CBER	Centre For Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CD4	Cluster of Differentiation 4
CD8	Cluster Determinant 8Cluster of Differentiation 8
CI	Confidence Interval
CIC	COVID-19 and Influenza Combination
CMA	Conditional Marketing Authorisation
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CSR	Clinical Study Report
DIBD	Development International Birth Date
DLP	Data Lock Point
ECDC	European Center for Disease Prevention and Control
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EoS	End of Study
EU	European Union
EU/mL	ELISA Units per mL
EUA	Emergency Use Authorisation
EUL	Emergency Use Listing

Acronym	Abbreviation Definition
Fc	Fragment Crystallizable Region
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
GMEU	Geometric Mean ELISA Unit
GMFRs	Geometric Mean Fold Rises
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titre
GMTR	Geometric Mean Titre Ratio
GVP	Good Pharmacovigilance Practices
HA	Health Authority
hACE2	Human Angiotensin Converting Enzyme 2
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
ICC	Influenza COVID Combination
ICD	International Classification of Disease
ICH	International Conference on Harmonisation
ICSR(s)	Individual Case Safety Report(s)
ID50	Inhibitory Dilution at a Concentration of 50%
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
ILD	Interstitial Lung Disease
IM	Intramuscular
IME	Important Medical Event
IQR	Interquartile Range
J-NDA	Japanese New Drug Application
KDCA	Korean Disease Control and Prevention Agency
m1273	mRNA-1273, Moderna
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAAE(s)	Medically attended adverse event(s)
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter(s)
MN_{50}	Microneutralization Assay of the Dilution to Achieve 50% Neutralization
mRNA	Messenger Ribonucleic Acid
n	Number
NA or N/A	Not Available or Not Applicable

Acronym	Abbreviation Definition
NDS	New Drug Submission
NAb	Neutralising antibody
NEC	Not Elsewhere Classified
NIH	National Institute of Health
NLS	Noble Life Sciences
NVX	Novavax, Inc.
NVX, CZ	Novavax, Czech Republic
O/E	Observed to Expected
OUHSC	University of Oklahoma Health Sciences Center
PAES	Post-Authorisation Efficacy Studies
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PIMMC(s)	Potential Immune Mediated Medical Condition(s)
PLWH	People Living with HIV
PP-EFF	Per Protocol-Efficacy
PP-IMM	Per Protocol Immunogenicity
PRAC	Pharmacovigilance Risk Assessment Committee
PSAR	Pandemic Special Access Route
PSUR	Periodic Safety Update Report(s)
PT(s)	Preferred Term(s)
qNIV	Quadrivalent Nanoparticle Influenza Vaccine
r	Recombinant
RBD+ MBC	Receptor-binding domain–specific Memory B cell
RMP	Risk Management Plan
RR	Rate Ratio
RSI	Reference Safety Information
S	Spike Protein
SAE(s)	Serious Adverse Event(s)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SARS-CoV-2 rS	Severe Acute Respiratory Syndrome Coronavirus 2, recombinant, adjuvanted
SER	Signal Evaluation Report
SIIPL / SII	Serum Institute of India PVT. LTD.
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC(s)	System Organ Class(es)
SRR(s)	Seroresponse rate(s)

Acronym	Abbreviation Definition
SSR	Summary Safety Report
TEAE(s)	Treatment Emergent Adverse Event(s)
TGA	Therapeutic Goods Administration
TNF	Tumor Necrosis Factor
TTO	Time to Onset
UK	United Kingdom
US	United States
V	Version
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VOC	Variants of Concern
VOI	Variants of Interest
VS	Versus
WHO	World Health Organisation
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the fifth Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™, summarising interval and cumulative safety data received by Novavax (NVX) for the reporting interval 20-Dec-2023 to 19-Jun-2024. This PBRER also includes exposure and safety data for Nuvaxovid™ XBB.1.5. As used in this report, the term "original vaccine" refers to Nuvaxovid, the term "updated vaccine" refers to Nuvaxovid XBB.1.5, and the term "Novavax COVID-19 vaccines" refers to both Nuvaxovid and Nuvaxovid XBB.1.5.

The format and content of this PBRER complies with the Guideline on GVP Module VII-Periodic safety update report (EMA/816292/2011 [Dec-2013]), the ICH Guideline E2C (R2) on PBRER [Step 5, Jan-2013]), the corePSUR19 guidance (EMA/362988/2021 [08-Jul-2021]), and the Consideration on core requirements for RMPs of COVID-19 vaccines - coreRMP19 guidance v3.1 (EMA/PRAC/709308/2022 [01-Sep-2022]). The periodicity of this PBRER is based on the European Union (EU) birth date (international birth date) of 20-Dec-2021, for Nuvaxovid.

NVX has developed recombinant Spike (rS) protein nanoparticle vaccines for active immunisation to prevent COVID-19 caused by SARS-CoV-2 and variants of concern. All SARS-CoV-2 rS nanoparticle vaccines contain purified recombinant Spike (rS) protein antigens stabilized in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components, elicit B-and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against COVID-19.

NVX developed 5 monovalent nanoparticle study vaccines (NVX-CoV2373, NVX-CoV2515, NVX-CoV2540, NVX-CoV2601 and NVX-CoV2705) containing components of original SARS-CoV-2 Wuhan strain, and variants Omicron BA.1, Omicron BA.5, Omicron XBB.1.5, or JN.1, respectively. Currently two of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373) and Nuvaxovid XBB.1.5 (NVX-CoV2601). In this report, the trade names, Nuvaxovid and Nuvaxovid XBB.1.5, are used when referring to these vaccines in the post-authorisation/post-marketing setting, while Novavax's study vaccine names, NVX-CoV2373 (or Prototype) and NVX-CoV2601, are used when referring to these vaccines in clinical trials. Table 1 below describes the properties of Nuvaxovid and Nuvaxovid XBB.1.5.

As of the data lock point (DLP) (19-Jun-2024), 1 NVX-sponsored clinical trial was completed and 7 NVX--sponsored clinical trials were ongoing. Participants in Novavax-sponsored clinical trials were either adults (≥ 18 years), adolescents (≥ 12 years to < 18 years) or paediatric (6 months to < 12 years).

Table 1: Properties of the original and updated vaccines, Nuvaxovid and Nuvaxovid XBB.1.5

Parameters	Nuvaxovid	Nuvaxovid XBB.1.5
Vaccine code	NVX-CoV2373	NVX-CoV2601
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5
Description	Colourless to slightly yellow and clear to mildly opalescent dispersion for injection.	
Composition	One Dose (0.5 mL) contains 5 µg of recombinant SARS-CoV-2 Spike protein produced by the recombinant DNA technology using a Baculovirus protein expression system (in an insect cell line derived from Sf9 cells of the Spodoptera frugiperda species) and 50 µg of the saponin-based adjuvant Matrix-M™ which contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of Quillaja saponaria Molina extract.	
Dosage Forms	Multi-Dose vial containing either 5 or 10 doses per vial	Multi-Dose vial containing 5 doses per vial
Indication	Active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.	
Dosage	Primary vaccination series: Administered intramuscularly as a course of 2 doses of 0.5 mL each. It is recommended to administer the second Dose 3 weeks after the first dose. Booster dose: Administered intramuscularly approximately 3 months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose) Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an mRNA vaccine or adenoviral vector vaccine (heterologous booster dose).	Administered intramuscularly as a single Dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. It should be administered at least 3 months after the most recent dose of a COVID-19 vaccine in individuals who have previously been vaccinated. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.,

Further details on the mechanism of action, indications, pharmaceutical form(s) and instructions for use are presented in the Company Core Data Sheets (CCDS) in Appendix 1, Appendix 2 and in the EU Summary of Product Characteristics (SmPC) in Appendix 3.

Additional safety topics and reporting requirements for countries/regions are presented as follows: Australia in Appendix 15, Canada in Appendix 16, the EU in Appendix 17, the United Kingdom (UK) in Appendix 18 and the United States (US) in Appendix 19.

2 WORLDWIDE MARKETING AUTHORISATION STATUS

Nuvaxovid:

Nuvaxovid has received marketing authorisation or has been authorised for emergency use as a two-dose primary series and as a booster for individuals 12 years and older, in multiple countries, the EU region and by the World Health Organisation (WHO), an agency of the United Nations. Alternative names for Nuvaxovid include Covovax™ (in countries where Serum Institute of India Pvt Ltd. (SIIPL) is the Marketing Authorisation Holder (MAH)) and Novavax COVID-19 Vaccine, Adjuvanted in the US. In India, Covovax is authorised as a two-dose primary series in individuals 7 years of age and older and as a booster for individuals 18 years of age and older. In Japan, Nuvaxovid is authorised as a two-dose primary series in individuals 6 years of age and older, and as booster in individuals 12 years of age and older. In addition, the WHO has granted authorisation for both Nuvaxovid and Covovax. Refer to Appendix 4, Table 31 for the Worldwide Marketing Authorisation (WWMA) Status.

During the reporting interval:

- Covovax received marketing authorisation in Brazil as a primary series for individuals 12 years and older.
- Nuvaxovid received marketing authorisation in Japan as a primary series for individuals aged 6 years and older.

Nuvaxovid XBB.1.5:

Nuvaxovid XBB.1.5 received authorisation for emergency use or received marketing authorisation for individuals 12 years and older in multiple countries, the EU region and by the WHO. Alternative names for Nuvaxovid XBB.1.5 include Covovax™ COVID-19 Vaccine Adjuvanted (2023-2024 Formula) in Brazil (where SIIPL is the MAH), Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) in the US and Novavax COVID-19 Vaccine 2023-2024 formula in South Korea.

During the reporting interval:

- Nuvaxovid XBB.1.5 received marketing authorisation in UK.
- Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula) received approval in Brazil.
- Nuvaxovid XBB.1.5 received approval in Singapore.

Additional details regarding the WWMA status are provided in Appendix 4 Table 32. Authorisations are pending in other regions.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

None.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the CCDS, Version (v) 9.0, effective date 19-Dec-2023 (Appendix 1). During the reporting interval, CCDS v9.0 was updated to v10.0 (effective date 30-May-2024) (Appendix 2). CCDS v10.0 served as the RSI from effective date to the end of the reporting interval.

4.1 Safety Variations

No safety variations were submitted during the reporting interval.

4.2 Summary of Changes to CCDS

A summary of changes to the CCDS from v9.0 to v10.0 is presented in Table 2 below.

Table 2: Summary of Changes to CCDS During the Reporting Interval

Location of Change	Summary of Changes
Section 1.2 – Common / Proper Name	Reference to INN removed; information about JN.1/2024-2025 Formula added to names list
Section 2 – Qualitative and Quantitative Composition	Completed missing information on active substance composition. Information about single-dose/multidose vials and single-dose pre-filled syringe added according to EMA-proposed product information. Information on JN.1 composition added. Additional text box on spike protein added. Note to local label preparer box on circulating strain added.
Section 4.2.1 – Dosing and Schedule	Information on JN.1 added. Alternate text box on 2-dose regimen added.
Section 4.6.1 – Pregnancy	JN.1 added to product reference.
Section 4.8.2 – Post-marketing experience	JN.1 added to product reference. Table 2: Deleted rows related to Ear and Labyrinth disorders and Tinnitus.
Section 6.3 – Shelf Life/Storage	Extended information with respect to single-dose vial and pre-filled syringe presentations.
Section 6.4 – Special Precautions for Storage	Pre-filled syringe presentation added.
Section 6.5 – Nature and Contents of Container	New single-dose vial and pre-filled syringe presentations added.
Section 6.6 – Instructions for Use/Handling	Extended information with respect to single-dose vial and pre-filled syringe presentations. Note to Local Labelling Preparer boxes added on storage deviation from EU labelling.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative Subject Exposure in Clinical Trials

Overall cumulative exposure in clinical trials is described in Table 3. Stratification by age, sex and race are provided in Table 4, Table 5 and Table 6, respectively.

Abbreviations for Novavax COVID-19 vaccines include:

Monovalent vaccines

- Prototype (NVX-CoV2373)
- BA.1 (NVX-CoV2515)
- BA.5 (NVX-CoV2540)
- XBB.1.5 (NVX-CoV2601)

Bivalent vaccines:

- Prototype + BA.1 (NVX-CoV2373 + NVX-CoV2515)
- Prototype + BA.5 (NVX-CoV2373 + NVX-CoV2540)
- Prototype + XBB.1.5 (NVX-CoV2373 + NVX-CoV2601)

COVID-19 and Influenza Combination (CIC) vaccine:

- Prototype (NVX-CoV2373) + qNIV (quadrivalent nanoparticle influenza vaccine)

Table 3: Cumulative Participant Exposure by Clinical Trial and Study Treatment

Clinical Trial	Number of Participants									
	Placebo	**BA.1**	**BA.5**	**CIC**	**Prototype**	**Prototype +BA.1**	**Prototype +BA.5**	**XBB.1.5**	**Blinded Treatment**	**Total (Excl. Placebo)**
2019nCoV-101 Part 1	23	–	–	–	108	–	–	–	–	108
2019nCoV-101 Part 2	254	–	–	–	1,029	–	–	–	–	1,029
2019nCoV-205	–	–	–	–	–	–	–	–	993	993
2019nCoV-301 Adult	3,458	–	–	–	26,124	–	–	–	–	26,124
2019nCoV-301 Peds	75	–	–	–	2,157	–	–	–	–	2,157
2019nCoV-302	4,346	–	–	–	10,792	–	–	–	–	10,792
2019nCoV-307	–	–	–	–	905	–	–	–	–	905
2019nCoV-311 Part 1	–	347	–	–	335	269	–	–	–	951
2019nCoV-311 Part 2	–	–	254	–	251	–	259	–	–	764
2019nCoV-312	–	–	43	–	104	–	–	–	–	147
2019nCoV-313	–	–	–	–	–	–	–	670	–	670
2019nCoV-314	–	–	–	–	–	–	–	–	400	400
2019nCoV-501	304	–	–	–	4,104	–	–	–	–	4,104
2019nCoV-503	–	–	–	–	–	–	–	–	3,682	3,682
2019nCoV-505	–	–	–	–	383	–	–	–	–	383
2019nCoV-ICC-E-101	–	–	–	558	78	–	–	–	–	636
2019nCoV-CIC-E-201	–	–	–	864	315	–	–	–	–	1,179
Total	**8,460**	**347**	**297**	**1,422**	**46,685**	**269**	**259**	**670**	**5,075**	**55,024** [1]

[1] Participants from the 2019nCoV-312 study (n=147) are a subset of the participants in the 2019nCoV-307 study and are counted twice.

Table 4: Cumulative Participant Exposure Stratified by Age

Age	Treatment/Number of Participants									
	Placebo	**BA.1**	**BA.5**	**CIC**	**Prototype**	**Prototype + BA.1**	**Prototype + BA.5**	**XBB.1.5**	**Blinded**	**Total (Excl Placebo)**
6 – < 24 months	–	–	–	–	–	–	–	–	1,206	1,206
2 – < 6 years	–	–	–	–	–	–	–	–	1,216	1,216
6 – < 12 years	–	–	–	–	–	–	–	–	1,260	1,260
12 – < 18 years	75	–	–	–	2,157	–	–	–	400	2,557
18 – 34 years	1,437	135	92	–	12,089	97	69	186	–	12,668
35 – 50 years	1,938	143	143	52	13,929	113	122	217	10	14,729
51 – 65 years	2,879	69	54	956	13,100	59	60	175	479	14,952
> 65 years	2,131	–	8	414	5,410	–	8	92	504	6,436
Total	**8,460**	**347**	**297**	**1,422**	**46,685**	**269**	**259**	**670**	**5,075**	**55,024** [1]

[1] Participants from the 2019nCoV-312 study (n=147) are a subset of the participants in the 2019nCoV-307 study and are counted twice.

Table 5: Cumulative Participant Exposure Stratified by Sex

Sex	Treatment/Number of Participants									
	Placebo	**BA.1**	**BA.5**	**CIC**	**Prototype**	**Prototype + BA.1**	**Prototype + BA.5**	**XBB.1.5**	**Blinded**	**Total (Excl Placebo)**
Male	4,343	155	133	586	24,196	118	120	272	2,475	28,055
Female	4,117	192	164	836	22,489	151	139	398	2,600	26,969
Total	**8,460**	**347**	**297**	**1,422**	**46,685**	**269**	**259**	**670**	**5,075**	**55,024** [1]

[1] Participants from the 2019nCoV-312 study (n=147) are a subset of the participants in the 2019nCoV-307 study and are counted twice.

Table 6: Cumulative Participant Exposure Stratified by Race

Racial Group	Treatment/Number of Participants									
	Placebo	**BA.1**	**BA.5**	**CIC**	**Prototype**	**Prototype +BA.1**	**Prototype +BA.5**	**XBB.1.5**	**Blinded**	**Total (Excl Placebo)**
Aboriginal Australian	–	–	–	1	3	–	–	–	–	4
American Indian or Alaska Native	199	–	–	2	1,846	–	–	12	137	1,997
Asian	314	48	39	43	1,767	39	26	14	922	2,898
Black or African American	598	1	16	-	7,971	–	–	200	983	9,171
Maori	–	–	–	14	2	–	–	–	–	16
Native Hawaiian or Other Pacific Islander	5	3	2	5	81	1	1	3	14	110
White or Caucasian	7,224	280	220	1,314	33,814	220	215	415	1,835	38,313
Other	12	10	14	17	149	8	14	4	1,148	1,364
Multiple	63	5	6	15	726	1	1	8	27	789
Missing or Not Reported	45	–	–	11	326	–	2	14	5	358
Unknown	–	–	–	–	–	–	–	–	4	4
Total	**8,460**	**347**	**297**	**1,422**	**46,685**	**269**	**259**	**670**	**5,075**	**55,024** [1]

[1] Participants from the 2019nCoV-312 study (n=147) are a subset of the participants in the 2019nCoV-307 study and are counted twice.

5.2 Cumulative and Interval Exposure in the Post-Authorisation Setting

Cumulative and interval post authorisation distribution and exposure data for Novavax Covid-19 vaccines are presented in Table 7 and stratified by country/region in Table 8.

Sources for administration and distribution data are summarised in Appendix 11.

Table 7: Overall Summary of Administration and Distribution of Novavax COVID-19 Vaccines

Timeframe	Nuvaxovid **		Nuvaxovid XBB.1.5 **		Novavax COVID-19 Vaccines	
	Administered	Distributed	Administered	Distributed	Administered	Distributed
Interval *	5,797	0	1,048,691	9,009,590	1,054,488	9,009,590
Cumulative	2,989,177	124,790,110	1,201,601	18,101,000	4,190,778	142,891,110

* Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source as indicated in Table 42.

** Includes Novavax and SIIPL products corresponding to the original and updated Novavax COVID-19 vaccines

Table 8: Interval and Cumulative Distribution and Administration Data for Novavax COVID-19 Vaccines from Post-Authorization Experience across Regions/License Partners and Strains

Country/Region (License Partner as applicable)	Nuvaxovid		Nuvaxovid XBB.1.5	
	Total Doses Administered	Total Doses Distributed	Total Doses Administered	Total Doses Distributed
Interval (20-Dec-2023 to 19-Jun-2024)				
Australia (Biocelect Pty Ltd.) [a]	2,010	0	0	0
Canada [a]	1,235	0	448	0
EU [a]	0	0	683,883	402,180
Germany [a]	0	0	Not available	7,803,990
India [b]	1,578	Not Available	0	0
Indonesia [b]	Not Available	Not Available	0	0
Israel (Medicalix/Freyr) [a]	Not Available	0	0	0
Japan (Takeda) [a]	974	0	0	0
New Zealand (Biocelect New Zealand Ltd) [a]	Not Available	0	0	0
Singapore (PharmEng Technology Pte Ltd) [a]	Not Available	0	0	25,000
South Korea (SK Bioscience) [a]	0	0	12,311	0
Switzerland [a]	0	0	0	0
Taiwan [a]	0	0	262,343	462,800
Thailand [b]	Not Available	Not Available	0	0
UK [a]	0	0	0	0

Table 8: Interval and Cumulative Distribution and Administration Data for Novavax COVID-19 Vaccines from Post-Authorization Experience across Regions/License Partners and Strains

Country/Region (License Partner as applicable)	Nuvaxovid		Nuvaxovid XBB.1.5	
	Total Doses Administered	Total Doses Distributed	Total Doses Administered	Total Doses Distributed
Interval (20-Dec-2023 to 19-Jun-2024)				
US [a]	0	0	89,706	315,620
Novavax Total (incl Takeda and SK Bio)	**4,219**	**0**	**1,048,691**	**9,009,590**
SIIPL Total	**1,578**	**Not Available**	**0**	**0**
Interval Total	**5,797**	**0**	**1,048,691**	**9,009,590**
Cumulative				
Australia (Biocelect Pty Ltd.) [a]	273,670	27,384,600	0	0
Canada [a]	37,343	9,749,000	448	125,000
EU [a]	355,807	25,603,900	683,899	6,054,480
Germany [a]	160,154	27,504,900	Not available	9,385,510
India [b]	54,933	126,250	0	0
Indonesia [b]	Not Available	9,008,000	0	0
Israel (Medicalix/Freyr) [a]	43	2,000,000	0	0
Japan (Takeda) [a]	349,779	8,238,590	0	0
New Zealand (Biocelect New Zealand Ltd) [a]	7,867	3,268,000	0	0
Singapore (PharmEng Technology Ltd) [a]	40,873	705,000	0	25,000
South Korea (SK Bioscience) [a]	974,574	2,932,470	12,311	504,000
Switzerland [a]	3,073	526,400	0	0
Taiwan [a]	640,584	1,805,200	262,343	462,800
Thailand [b]	Not Available	200,000	0	0
UK [a]	1,282	1,000,000	0	0
US [a]	89,195	4,737,800	242,600	1,544,210
Novavax Total (incl Takeda and SK Bio)	**2,934,244**	**115,455,860**	**1,201,601**	**18,101,000**
SIIPL Total	**54,933**	**9,334,250**	**0**	**0**
Cumulative Total	**2,989,177**	**124,790,110**	**1,201,601**	**18,101,000**

[a] Novavax as MAH

[b] SIIPL as MAH

6 DATA IN SUMMARY TABULATIONS

Data in summary tabulations include serious adverse events (SAEs) from NVX-sponsored clinical trials, and serious/non-serious adverse drug reactions (ADRs) in the post--authorisation setting.

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), v27.0 was used for the coding of SAEs and ADRs.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 5 presents overall cumulative summary tabulations of treatment-emergent SAEs from NVX-sponsored interventional clinical trials of NVX-CoV2373, NVX-CoV2515, NVX-CoV2540 and NVX-CoV2601 from the development international birth date (DIBD) (23-Apr-2020) to the DLP (19-Jun-2024) of the PBRER. This appendix includes SAEs originating from the following NVX-sponsored studies: 2019nCOV-101, 2019nCOV-205, 2019nCOV-301, 2019nCOV-302, 2019nCOV-307, 2019nCOV-311, 2019nCOV-312, 2019nCOV-313, 2019nCOV-314, 2019nCOV-501, 2019nCOV-503 and 2019nCOV-505.

Data are extracted from the NVX global safety database and may contain unblinded information and are presented by MedDRA System Order Class (SOC) and Preferred Term (PT). Both active and placebo treatments may be identified as suspect products for an event occurring in an individual participant where the event hazard window is considered to overlap with both treatments. Therefore, the event count obtained by summing the data across rows may not match the data in the total column.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

Appendix 6 presents interval and cumulative counts of serious and non-serious adverse reactions for all spontaneous, regulatory authority, literature sources, and serious adverse reactions from non-interventional studies. All Individual Case Safety Reports (ICSRs) received reflect the version valid at the time of the DLP.

Appendix 6 A: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Authorisation Data Sources for Nuvaxovid

Appendix 6 B: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Authorisation Data Sources for Nuvaxovid XBB.1.5

6.3.1 Overview of Interval and Cumulative Post-Authorisation Data for Nuvaxovid and Nuvaxovid XBB.1.5

Table 9 summarises all post-authorisation ICSRs in the database that were approved during the reporting interval and cumulatively.

Note: Appendix 6 presents interval and cumulative serious and non-serious ADRs from post-marketing data sources in accordance with GVP Module VII. B.5.20 *Appendices to the PSUR*. Counts in this section include all adverse events (AEs) (irrespective of causality) therefore counts in this section may not align with the counts presented in Appendix 6.

Table 9: Overview of Interval and Cumulative ICSRs and AEs for Novavax COVID-19 Vaccines

Parameters		**Nuvaxovid (Cumulative administered doses = 2,989,177)**		**Nuvaxovid XBB.1.5 (Cumulative administered doses = 1,201,601)**	
		Interval [1]	**Cumulative**	**Interval [1]**	**Cumulative**
Number of ICSRs		174 (106 initial, 68 follow-up)	5,154	355 (336 initial, 19 follow-up)	498
Serious ICSRs (including fatal)		44	1,009	55	66
Non-Serious ICSRs		130	4,145	300	432
Fatal ICSRs		3 (1 initial, 2 follow-up)	34	8 (7 initial, 1 follow-up)	8
Number of AEs		680	18,386	1,472	1,878
Serious AEs		184	2,846	157	169
Non-serious AEs		496	15,540	1,315	1,709
Number of ICSRs classified by age group	Foetus [2]	–	1	1	2
	Neonate [2]	–	3	1	1
	Infant	–	1	–	–
	Child	–	8	–	2
	Adolescent	1	66	3	5
	Adult	93	3,732	108	160
	Elderly	29	729	65	97
	Unknown	51	614	177	231

[1] Includes both initial and follow-up counts

[2] Secondary exposure during pregnancy

6.3.2 Aggregate Adverse Event Data from South Korea

Nuvaxovid was authorised in South Korea on 12-Jan-2022 as a Biologics License Application by SK Bioscience Co., Ltd. On 29-Nov-2023, the Ministry of Food and Drug Safety in the

Republic of Korea granted Emergency Use Authorisation (EUA) for Novavax COVID-19 Vaccine 2023-2024 formula.

The Korean Disease Control and Prevention Agency (KDCA) publishes the COVID-19 Vaccine Safety Report, which includes cumulative aggregate safety data for Nuvaxovid. Since up-to-date individual case-level information is not available for downloading into the NVX safety database, the aggregate data is reviewed separately.

This section summarises cumulative safety data from the COVID-19 Vaccine Safety Report [KDCA 2022] (Week 169) covering the period from 26-Feb-2021 to 25-May-2024. As per the report, a total of 974,574 Nuvaxovid doses and a total of 12,311 doses of Novavax COVID-19 Vaccine 2023-2024 formula were administered cumulatively with a corresponding total of 1,296 and 4 AEs reported respectively.

Note: The periodic 6-month batch of AEs entered into the NVX global safety database from the Korea Institute of Drug Safety and Risk Management database represented in other data/analysis sections of this document has a reporting interval up to 31-Dec-2023. Because aggregate data from the KDCA report includes safety information up to 25-May-2024, the counts in this section will not align with other sections of the document. NVX will continue to add the South Korean ICSR data from Korea Institute of Drug Safety and Risk Management to the global safety database as it is made available and will also continue to summarise in this section the most up-to-date aggregate data available from the KDCA. Table 10 and Table 11 are excerpted directly from the KDCA report, including footnotes, if any.

6.3.2.1 Adverse Events in South Korea Following Immunisation by Novavax COVID-19 Vaccines Listed by Symptoms

Table 10: Cumulative Number of Cases Reporting Adverse Events/Cases following Administration of Novavax COVID-19 Vaccines in South Korea

Symptoms Suspected to be Adverse Events (including duplicates) **	Number of Cases	
	Nuvaxovid	Novavax COVID-19 Vaccine 2023-2024 formula
Myalgia	278	1
Headache	258	0
Dizziness	180	0
Chest pain	172	0
Allergic reaction	170	2
Vaccination Site Pain, Rash, Swelling within 3 days of vaccination	137	0
Queasy	118	0
Dyspnoea (Breathlessness)	101	0
Itching	90	0

Table 10: Cumulative Number of Cases Reporting Adverse Events/Cases following Administration of Novavax COVID-19 Vaccines in South Korea

Symptoms Suspected to be Adverse Events (including duplicates) **	Number of Cases	
	Nuvaxovid	Novavax COVID-19 Vaccine 2023-2024 formula
Chills	88	0
Pyrexia	79	1
Vomiting	53	0
Cellulitis (Inflammation at the injection site, not an abscess)	39	0
Abdominal pain	38	0
Lymph gland infection	32	0
Diarrhoea	32	0
Abnormal uterine bleeding	29	0
Arthritis	29	0
Severe local adverse reactions	16	0
Acute paralysis	14	0
Anaphylactoid reaction	8	0
Acute Cardiovascular injuries	7	1
Vaccine associated enhanced disease	7	0
Anaphylactic reaction	4	0
Vaccination site abscess	4	0
Alopecia *	3	0
Encephalopathy or Encephalitis	3	0
Guillain-Barre syndrome	3	0
Thrombosis	3	0
Visual acuity reduced *	3	0
Acute aseptic arthritis	1	0
Acute liver injury	1	0
Acute renal injury	1	0
Anosmia	1	0
Convulsion (Convulsion/Seizure)	1	0
Multiple Organ inflammatory syndrome	1	0

* The number of the "Alopecia" and "Visual acuity reduced" cases were calculated by KDCA by including the reported cases which contained the keyword "Alopecia" and "Visual acuity" respectively in the "Other Detailed Information" section in the "Adverse Event Report form". Thus, the numbers could be inaccurate.

** Two or more symptoms may be reported at the same time in a single reported case.

6.3.2.2 General Characteristics of Adverse Events which Resulted in Death in South Korea

Characteristics of case reports with fatal events are summarised in Table 11. No new fatal events have been reported and data remains unchanged from the previous PBRER.

Table 11: Characteristics of South Korean cases with fatal outcomes

Characteristics	Cases reported with Nuvaxovid
Total	13
Sex	
Male	7
Female	6
Age range in years	
10 – 19	0
20 – 29	1
30 – 39	0
40 – 49	0
50 – 59	1
60 – 69	3
70 – 79	3
≥ 80	5
Underlying Medical Conditions	
Yes	12
No	1
Time from Vaccination to Death	
< 1 day	1
1 day	0
2 days	1
≥ 3 days	11
Autopsy	
Done	0
Not Done	13

The aggregate data from South Korea is consistent with the global safety profile of Nuvaxovid, and no new signals have been identified by NVX or the KDCA as of the week 169 KDCA report.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

This section summarises clinically important efficacy (when provided), immunogenicity and safety findings from NVX-sponsored interventional clinical trials, with monovalent and/or bivalent Novavax study vaccines, which were ongoing or completed during the 6-month reporting interval for this PBRER (20-Dec-2023 to 19-Jun-2024). Table 12 below summarizes the Study IDs, study sites, vaccines, posology (2-dose primary series, booster dose or single dose), study populations, study status and whether an interim or final clinical study report (CSR) became available as of the DLP (19-Jun-2024) for this PBRER.

As of the DLP for this PBRER (19-Jun-2024), two parts of a 4-part clinical trial (Study 2019nCoV-301 Adult Main and Adult Booster), one part of a 2-part clinical trial (Study 2019nCoV-311 Part 1) and one other clinical trial (Study 2019nCoV-505) were completed. Also, as of the DLP for this PBRER, 7 clinical trials (of which one is a 4-part clinical trial and one is a 2-part clinical trial) were ongoing: 2019nCoV-205, 2019nCoV-301 (Adolescent Main and Adolescent Booster), 2019nCoV-311 Part 2, 2019nCoV-312, 2019nCoV-313 (Parts 1 and 2), 2019nCoV-314 and 2019nCoV-503.

Additional details, including control arms, for the completed and ongoing NVX-sponsored studies are summarized in Table 34 and Table 35 of Appendix 8.

Table 12: Overview of Clinical Trial Vaccines, Study Populations and Status as of the DLP (19-Jun-2024)

Study ID **Study location**	**Study Vaccine(s) / 2-dose Primary Series, Booster or Single dose**	**Study Population**	**Status as of the DLP (19-Jun-2024)**
2019nCoV-205 US	Prototype (NVX-CoV2373) or XBB.1.5 (NVX-CoV2601) / Heterologous booster	Adults ≥ 50 years previously vaccinated with COVID-19 mRNA vaccines	Ongoing
2019nCoV-301 (4 Parts)			
2019nCoV-301 Adult Main Mexico, US	Prototype (NVX-CoV2373) / Primary series	Healthy and medically stable adults ≥ 18 years	Completed
2019nCoV-301 Adult Booster Mexico, US	Prototype (NVX-CoV2373) / Homologous booster	Healthy and medically stable adults ≥ 18 years	Completed
2019nCoV-301 Adolescent Main US	Prototype (NVX-CoV2373) / Primary series	Adolescents 12 years to < 18 years	Ongoing

Table 12: Overview of Clinical Trial Vaccines, Study Populations and Status as of the DLP (19-Jun-2024)

Study ID **Study location**	**Study Vaccine(s) / 2-dose Primary Series, Booster or Single dose**	**Study Population**	**Status as of the DLP (19-Jun-2024)**
2019nCoV-301 Adolescent Booster US	Prototype (NVX-CoV2373) / Homologous booster	Adolescents 12 years to < 18 years	Ongoing
2019nCoV-311 (2 parts)			
2019nCoV-311 Part 1 Australia	Monovalent: Prototype (NVX-CoV2373) OR BA.1 variant-specific (NVX-CoV2515) / Heterologous booster (1 dose) Bivalent: Prototype+BA.1 (site-mixed NVX-CoV2373 + NVX-CoV2515) / Homologous Booster (1 dose)	Adults 18 to ≤ 64 years who previously received 2 doses of the Moderna and/or Pfizer/BioNTech prototype vaccines ≥ 180 days or 3 doses of the Moderna and/or Pfizer/BioNTech prototype vaccines ≥ 90 days prior to study vaccination	Completed
2019nCoV-311 Part 2 Australia	Monovalent: Prototype (NVX-CoV2373) OR BA.5 variant-specific (NVX-CoV2540) / Heterologous booster (2 doses) Bivalent: Prototype+BA.5 (site-mixed NVX-CoV2373 + NVX-CoV2540) / Heterologous Booster (2 doses)	Adults ≥ 18 years who previously received ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA vaccines ≥ 90 days prior to study vaccination	Ongoing
2019nCoV-312 US	Prototype (NVX-CoV2373) / Heterologous booster (1 dose)	Medically stable male and non-pregnant females who received a first booster of NVX-CoV2373 in Study 2019nCoV-307* (18 years to 49 years) following prior priming and booster doses with mRNA vaccines.	Ongoing

Table 12: Overview of Clinical Trial Vaccines, Study Populations and Status as of the DLP (19-Jun-2024)

Study ID **Study location**	**Study Vaccine(s) / 2-dose Primary Series, Booster or Single dose**	**Study Population**	**Status as of the DLP (19-Jun-2024)**
2019nCoV-313 (2 Parts)			
2019nCoV-313 Part 1 US and US territories	XBB.1.5 (NVX-CoV2601) / Heterologous booster	Medically stable male and non-pregnant females who are ≥ 18 years and vaccinated with ≥ 3 doses of the Moderna and/or Pfizer /BioNTech prototype monovalent and/or BA.4/5 containing bivalent COVID-19 vaccines. Participants last mRNA vaccination must have been administered ≥ 90 days prior to study vaccination.	Ongoing
2019nCoV-313 Part 2 US and US territories	XBB.1.5 (NVX-CoV2601) / Single dose	Medically stable male and non-pregnant females ≥ 18 years, who were baseline SARS-CoV-2 seropositive and COVID-19 vaccine naïve	Ongoing
2019nCoV-314 US	Monovalent: XBB.1.5 (NVX-CoV2601) / Heterologous booster Bivalent: Prototype+XBB.1.5 (site-mixed NVX-CoV2373+ NVX-CoV2601) / Heterologous booster	Previously vaccinated adolescents 12 years to < 18 years who received ≥ 2 doses of Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days prior to study vaccination.	Ongoing
2019nCoV-503 Colombia, Dominican Republic, Guatemala, Honduras, Mexico, Philippines, South Africa, Spain, UK, US	Prototype (NVX-CoV2373) / Primary series	Children 6 years to < 12 years, 2 years to < 6 years, and 6 months to < 24 months	Ongoing
2019nCoV-505	Prototype (NVX-CoV2373) / Primary series	People living with HIV and (Human Immunodeficiency Virus (HIV)-negative adults 18 to 65 years	Completed

* Study 2019nCoV-307 was a completed phase 3 study that compared the immunogenicity and safety of three lots of NVXCoV2373 in adults to demonstrate the consistency of effect among the 3 manufacturing lots of drug product.

7.1 Completed Clinical Trials

As of the DLP for this PBRER (19-Jun-2024), two parts of a 4-part clinical trial (2019nCoV-301 Adult Main and Adult booster), one part of a 2-part clinical trial (Study 2019nCoV-311 Part 1) and one clinical trial (Study 2019nCoV-505) were completed. Summaries of clinically important immunogenicity and safety results obtained from final CSRs are summarized below. No new clinically important safety information emerged from these trials during the reporting interval.

7.1.1 Study 2019nCov-301 Adult Main and Adult Booster

A Phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant (also referred to as NVX-CoV2373) in adult participants ≥ 18 years of age in the US and Mexico (Adult Main Study) with a Pediatric Expansion in adolescents 12 to < 18 years of age and a Booster Amendment and Second Booster Vaccination Sub-study.

The following information was obtained from the 24-month final CSR which presented results from both the Adult Main and Adult Booster parts of Study 2019nCoV-301. Results from the Pediatric Expansion parts will be presented in a separate future report.

The study was initiated on 27-Dec-2020 (first participant screened) and completed enrolment into the initial vaccination period on 18-Feb-2021. The blinded crossover vaccination period was initiated on 20-Apr-2021, and the first and second booster vaccination periods were initiated on 13-Dec-2021 and 19-Sep-2022, respectively. The date of the last participant, last visit for the final (24-month) analysis for Study 2019nCoV-301 was 10-Apr-2023, with database lock on 20-Dec-2023. The study was initiated under Clinical Protocol 2019nCoV-301 - v3.0, dated 16-Nov- 2020 and was operating under Clinical Protocol 2019nCoV-301 - v13.0, dated 15- Dec-2022 at the time of last participant, last visit.

Analysis of the primary and key secondary efficacy endpoints was performed on 01-Jun-2021. The evaluation of all statistical hypotheses for efficacy was completed as part of this analysis. Efficacy and safety data through the 01-Jun-2021 cutoff were described in the 2019nCoV-301 Interim Report, dated 09-Aug-2021. The interim report excluded immunogenicity data, because immunogenicity testing results were not available at the time of the report authoring. Immunogenicity data from the 01-Jun-2021 data cut were analyzed at a later date (09-Aug-2021). This report also excluded data from the blinded crossover vaccination period. For the primary endpoint, a protocol-specified unblinded aggregate analysis was performed using the accumulated 77 cases of polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 in adult participants serologically and virologically negative (to SARS-CoV-2 via anti-nucleocapsid protein [NP] serology and PCR testing, respectively) at baseline with onset from at least 7 days after second vaccination. The study remained blinded at the participant level for study site personnel and study participants through the end

of study (EoS), while the Sponsor was unblinded at the participant level at the time of the 01-Jun-2021 analysis to prepare for regulatory submissions.

Updates to the analysis of the primary and key secondary efficacy endpoints were performed at times of subsequent regulatory submissions using updated data extracts without formal statistical hypothesis testing, these updates were intended to be supportive in nature. A supportive update of the efficacy primary and key secondary endpoints and analysis of remaining efficacy endpoints was performed based on the EoS database lock data and these analyses are presented within this report.

An ad-hoc booster analysis was conducted in a subset of participants to assess immune response in a selected subset of participants immediately prior to and at 28 days after administration of the first NVX-CoV2373 booster dose and to assess safety through 28 days after the first NVX-CoV2373 booster dose (data cut date 15-Mar- 2022). These data are presented in the 2019nCoV-301 Adult Booster Report, dated 05-Aug-2022. An updated analysis of booster immunogenicity for this subset of participants and an expanded analysis of safety for all participants who received the first NVX-CoV2373 booster dose was conducted based on a 26-Mar-2022 data cut and these data were presented in the 2019nCoV-301 Adult Booster Report Addendum, dated 16-Dec-2022. An analysis of immunogenicity and safety in the Second Booster Sub-study was conducted when the 28-day sub-study period was complete (data cut 08-Nov-2022).

Safety data were updated cumulatively through the EoS Analysis. No new safety signals were identified. Safety data across all vaccination periods through the EoS database lock are presented in this report.

7.1.1.1 Efficacy Conclusions

Analysis of the primary and key secondary efficacy endpoints was performed on 01-Jun-2021. The evaluation of all statistical hypotheses for efficacy was completed as part of this analysis. Efficacy and safety data through the 01-Jun-2021 cutoff were described in the 2019nCoV-301 Interim Report dated 09-Aug-2021, which was submitted to the EMA in support of a CMA.

Updates to the analysis of the primary and key secondary efficacy endpoints were performed at times of subsequent regulatory submissions using updated data extracts without formal statistical hypothesis testing, these updates were intended to be supportive in nature. A supportive update of the efficacy primary and key secondary endpoints and analysis of remaining efficacy endpoints was performed based on the EoS database lock data and these analyses are presented within this report.

A two-dose primary regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart in the initial vaccination period, met the prespecified study success criterion of the primary efficacy outcome measure versus placebo in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset

from at least 7 days after second vaccination in seronegative (to SARS-CoV-2) adult participants.

- Primary efficacy based on the CMA Analysis, 01-Jun-2021 data cut: statistically significant Vaccine Efficacy (VE) = 90.40% (95% CI: 82.88, 94.62) for the primary endpoint; p-value < 0.001
- Updated supportive analysis (EoS Analysis) for the primary efficacy endpoint consistent with CMA analysis: Based on the EoS analysis: VE = 91.53% (95% CI: 83.31, 95.70)
- High VEs for the following subgroups of the primary endpoint based on the CMA Analysis:
  - Participants 18 to < 65 years of age: 91.50% (95% CI: 84.21, 95.42)
  - High-risk participants: 90.96% (95% CI: 83.57, 95.03)
  - Male participants: 90.89% (95% CI: 76.03, 96.54)
  - Female participants: 89.99% (95% CI: 79.36, 95.14)
  - White participants: 89.37% (95% CI: 79.99, 94.35)
  - Non-White participants: 93.57% (95% CI: 71.68, 98.54)
  - Black or African American participants: 100.00% (95% CI: 67.86, 100.00)
  - American Indian or Alaska Native participants: 100.00% (95% CI: -143.63, 100.00)
  - Asian participants: 100.00% (95% CI: 52.81, 100.00)
  - Hispanic or Latino participants: 67.28% (95% CI: 18.65, 86.84)
  - Not Hispanic or Latino participants: 95.08% (95% CI: 88.54, 97.89)
  - US: 90.36% (95% CI: 82.78, 94.60)
  - Comorbidity status, no: 89.94% (95% CI: 77.05, 95.59)
  - Comorbidity status yes: 90.76 (95% CI: 79.16, 95.90)
  - There were too few cases of COVID-19 for the remaining demographic characteristics and COVID-19 risk conditions to allow meaningful interpretation of VE.
- Subgroup analyses were confirmed based on the EoS Analysis
- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant not considered a VOC or variant being monitored with onset from at least 7 days after second vaccination in seronegative (to SARS-CoV-2) adult participants.
- CMA Analysis: VE = 100.00% (95% CI: 80.75, 100.00), due to a SARS-CoV-2 variant not considered as a VOC or variant being monitored.
- Confirmed with the EoS Analysis: VE = 97.18% (95% CI: 78.65, 99.63).

- NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination in seronegative (to SARS-CoV-2) adult participants with no moderate or severe cases of COVID-19 among NVX-CoV2373 recipients.
- CMA Analysis: VE=100.00% (95% CI: 86.99, 100.00)
- Confirmed with the EoS Analysis: VE = 100.00% (95% CI: 84.78, 100.00)

Cumulative rates of PCR-confirmed symptomatic mild, moderate, and severe COVID-19 began to diverge at approximately 21 days after first vaccination. Cumulative rates of PCR-confirmed symptomatic moderate and severe COVID-19 began to diverge at approximately 3 months after first vaccination.

7.1.1.2 Immunogenicity Conclusions

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered 21 (+ 7) days apart, markedly increased wild-type virus (ancestral Wuhan strain) neutralizing antibody, serum IgG antibody, hACE2 receptor binding inhibition antibody levels relative to placebo in adult participants ≥ 18 years of age regardless of baseline serostatus. Greater immune responses were observed in younger adult participants (18 to < 65 years of age) than in older adult participants (≥ 65 years of age) but with high SCRs across the age groups.

A single booster dose of NVX-CoV2373, administered at a minimum of 6 months after the primary series of NVX-CoV2373 in adult seronegative participants, elicited robust immune responses (neutralizing antibodies, serum IgG antibodies, and hACE2 receptor binding inhibition) against the wild-type virus (ancestral Wuhan strain) at 28 days after booster vaccination that were higher than those reported at 14 days after primary series vaccination in adult participants. Sustained immune responses were observed through 240 days after the booster dose. Immune responses after a second booster dose of NVX-CoV2373 were comparable to those following the first booster.

NVX-CoV2373 elicited robust Type 1 T helper pathway responses on Day 21 (21 days after first vaccination) and Day 35 (14 days after second vaccination) which were markedly increased relative to placebo.

7.1.1.3 Safety Conclusions

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart, followed by a booster dose administered ≥ 6 months after completion of the primary series was well tolerated and had an acceptable safety profile in adult participants ≥ 18 years of age.

Approximately 97% of NVX-CoV2373 recipients received both doses of trial vaccine in the initial vaccination period, with 97.3% of participants 18 to < 65 years of age and 93.3% of

participants ≥ 65 years of age receiving both doses of NVX-CoV2373. Of the participants who crossed over to receive the opposite treatment during the blinded crossover vaccination period, 99% received both doses of trial vaccine, with 98.8% of participants 18 to < 65 years of age and 99.7% of participants ≥ 65 years of age crossing over from placebo in the initial vaccination period to receive both doses of NVX-CoV2373 during the blinded crossover vaccination period. A total of 13,354 participants continued on to receive a booster dose of NVX-CoV2373 a median of 11.0 months after receiving the second dose of NVX-CoV2373 in either the initial or blinded crossover vaccination period. A total of 359 participants received a second booster dose of NVX-CoV2373

The median duration of safety follow-up was 2.5 months after the second vaccination in the initial vaccination period, 8.4 months after second vaccination in the blinded crossover vaccination period, and 11.9 months after the booster dose.

During the initial vaccination period, NVX-CoV2373 recipients reported higher frequencies and intensities of solicited injection site and systemic TEAEs than placebo recipients, especially after the second vaccination of the initial vaccination period (solicited TEAEs were not recorded during the blinded crossover vaccination period). This trend was observed in both age cohorts, 18 to < 65 years of age and ≥ 65 years of age, with lower frequencies and intensities of solicited injection site and systemic TEAEs in the older age cohort.

The median onset for solicited local injection site and systemic TEAEs reported in both NVX-CoV2373, and placebo was Day 2, with a median duration of 2 or 3 days in the NVX-CoV2373 group. TEAEs that persisted beyond the 7-day reactogenicity period were reported more frequently in the NVX-CoV2373 group than in the placebo group.

Most solicited local injection site and systemic TEAEs were grade 1 or 2 in intensity, with grade 3 or 4 local injection site TEAEs reported in less than 10% of NVX-CoV2373 recipients and grade 3 or 4 systemic TEAEs reported in less than 15% of NVX-CoV2373 recipients. Tenderness and pain were the most frequently reported local injection site TEAEs, and fatigue, headache, myalgia, and malaise were the most frequently reported systemic TEAEs.

For NVX-CoV2373 recipients the frequency and intensity of solicited injection site and systemic TEAEs increased from Dose 1 to Dose 2 in the initial vaccination period. Following administration of a booster dose of NVX-CoV2373 the frequency of solicited injection site and systemic TEAEs was similar to that observed following the second dose; however, although most TEAEs remained grade 1 or 2 in severity following the booster dose, there was an increase in the frequency of grade ≥ 3 TEAEs. Following the booster dose tenderness and pain were the most frequently reported (incidence > 10%) solicited local injection site TEAEs and fatigue, myalgia, headache, malaise, arthralgia, and nausea/vomiting were the most frequently reported (incidence > 10%) solicited systemic TEAEs. Among NVX-CoV2373 booster recipients, there were lower frequencies and intensities of solicited local injection site and systemic TEAEs in participants ≥ 65 years of age than in participants 18 to < 65 years of age.

Frequencies of SAEs were generally low across the NVX-CoV2373 and placebo groups with similar frequencies between the 2 vaccine groups. During the initial vaccination period, SAEs were reported for 1.2% of NVX-CoV2373 recipients and 1.3% of placebo recipients. The frequency of SAEs was 2.8% for participants crossing over to receive NVX-CoV2373 and 2.7% for participants crossing over to receive placebo during the blinded crossover period. Within the 11.9 months of median follow-up following the booster dose, 3.0% of participants reported SAEs.

The frequencies of SAEs of myocarditis and pericarditis remained low (< 0.1%) through the EoS. The incidence of death remained low (≤ 0.2%) and balanced among NVX-CoV2373 and placebo recipients, none of the events of death reported were related to vaccination. The frequency of Potential Immune Mediated Medical Conditions (PIMMCs) based on investigator reporting and protocol-defined criteria was ≤ 0.2% and the frequency of COVID-19 related TEAEs remained < 0.1% during each of the vaccination periods and across all treatment groups.

7.1.1.4 Overall Conclusions for Completed Study 2019nCoV-301 Adult Main and Adult Booster

The data presented in this report represent the clinical data for participants ≥ 18 years of age in Study 2019nCoV-301 from the initiation of the study to the EoS database lock.

The calendar period during which these data were collected represented a challenging backdrop for the conduct of a randomized clinical trial. Enrollment and dosing commenced on 27-Dec-2020, at the same time that EUA COVID-19 vaccinations became available in the US and recommended for individuals at high risk for acquisition or complications of COVID-19. Over the subsequent months, EUA vaccines became available for larger groups of the public until 20-Apr-2021, when vaccines were recommended for all adults 18 years of age and older in the US.

As a result of these public health recommendations, measures were implemented to enroll the entire study, while focusing less on the elderly and healthcare providers and more on individuals with other risk factors and racial and ethnic characteristics that also needed access to vaccination. Because of the availability of EUA vaccination for all adults in the US, a blinded crossover was implemented to assure active vaccination for all participants in an effort to retain participants and allow the continued collection of long-term safety data while remaining blinded to treatment assignment. Nonetheless, a significant proportion of study participants were lost to follow-up for absolute efficacy estimates due to their desire to receive an EUA vaccine, even though the number of participants remaining in safety follow-up remained sufficient to assess the safety profile of the NVX-CoV2373.

Another challenge facing the analysis of the study has been the evolution of the pandemic and emergence of new variants. During the placebo-controlled portion of the study, prior to the blinded crossover, the Alpha variant became predominant in the US, resulting in an

assessment of absolute efficacy of the vaccine not against the ancestral strain that was the basis used to manufacture the vaccine, but rather largely against the Alpha variant. Over the ensuing months, the evolution continued with the emergence of new variants, further complicating the assessment of efficacy. The incidence rates of cases following crossover and following a booster dose of NVX-CoV2373 have been calculated and statistical approaches to further assess efficacy have been developed. Of note, immunogenicity analyses demonstrated that antibody titers are higher following a booster dose of NVX-CoV2373 than after the primary series and it is expected that a booster dose of NVX-CoV2373 will provide continued protective efficacy.

These challenges have required the implementation of several modifications to the trial, most obviously, the blinded crossover vaccination period. The key secondary efficacy endpoint was also modified to focus on variants not of concern or interest to, as much as feasible, assess the efficacy against the ancestral viral strain. Assessment of efficacy against the variants of interest/concern, especially the Alpha variant demonstrated a high level of efficacy against these variants.

This report presents the full efficacy dataset of all participants with protocol-defined primary endpoint cases of mild, moderate, or severe COVID-19 through the initial vaccination period (i.e., placebo-controlled portion of follow-up) and has demonstrated that there is no substantive change in absolute efficacy from that presented in the 2019nCoV-301 Interim Report dated 09-Aug-2021 for CMA, which met the prespecified criteria of VE $\geq$ 50% with lower bound of 95% CI > 30%, demonstrating the efficacy of a 2-dose regimen of NVX-CoV2373 in the prevention of mild, moderate, or severe COVID-19.

Immunogenicity testing 14 days after the primary vaccination series were used to establish the vaccine's induction of a robust immune response in terms of neutralizing antibody titers, anti-spike IgG levels and hACE2 receptor binding inhibition levels. Serum samples were also tested by independent, US Government-sponsored labs and analyzed by an independent NIH-sponsored team to define levels of antibodies that correlated with protection against symptomatic COVID-19 [Fong 2023]. These data were also used to evaluate the likelihood of protective efficacy that could be expected from the level of immune response that followed the booster injection $\geq$ 6 months after the primary series. Across all 3 assay types and the timepoints at which they were measured, the immunogenicity of the vaccine was supportive of the clinical efficacy described.

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart, followed by a booster dose administered $\geq$ 6 months after completion of the primary series was well tolerated and had an acceptable safety profile in adult participants $\geq$ 18 years of age.

The efficacy, immunogenicity, and safety profile of NVX-CoV2373 demonstrated in this trial is considered to be supportive of licensure of this product for active immunization of adults 18 years of age and older.

7.1.2 Study 2019nCoV-311 Part 1

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

Study 2019nCoV-311 was a multi-part, Phase 3, randomized, observer-blinded study conducted in Australia, evaluating the safety and immunogenicity of Omicron subvariant vaccines in adult participants. Part 1 evaluated a single booster dose of NVX-CoV2515 and NVX-CoV2373 alone and bivalent prototype and Omicron subvariant vaccine (NVX-CoV2373 + NVX-CoV2515) in previously vaccinated adults 18 to 64 years of age (inclusive) in Australia (Protocol 2019nCoV-311 [v6.0, dated 01-Feb-2023] and Statistical Analysis Plan [v5.0, dated 21-Dec-2023]). Participants were previously vaccinated with 2 (Groups A and B) or 3 (Groups C, D, and E) doses of the Moderna and/or Pfizer-BioNTech prototype vaccines. Part 1 was initiated on 31-May-2022 (first participant screened) and completed enrolment on 17-Jul-2022; study enrolment was halted due to achieving the necessary number of participants to assess the primary objective, which was to determine if NVX-CoV2515 induces superior antibody responses to the Omicron BA.1 subvariant compared to the antibody response induced by NVX-CoV2373 in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer/BioNTech prototype vaccines).

Part 1 immunogenicity and safety data through Day 28 for participants enrolled in Groups C, D, and E were presented in the 2019nCoV-311 Interim Analysis v1.0, dated 07-Mar-2023 with a data cutoff date of 01-Sep-2022. The final CSR summarized the results of Part 1 through the end of the study with a data extraction date of 18-Oct-2023. Data presented in the final CSR for Group C, D, and E participants focus on new data since the time of the interim analysis with select interim data re-iterated (e.g., the primary endpoint) or referenced for relevant comparisons. Data for Group A and B participants are presented for the first time in the final CSR.

7.1.2.1 Immunogenicity Conclusions

The primary objective of the study was met, achieving both co-primary endpoints needed to demonstrate that the Omicron BA.1 specific vaccine (NVX-CoV2515) produced a superior antibody response to the Omicron BA.1 subvariant when compared to the prototype vaccine (NVX-CoV2373) at Day 14. Microneutralization (MN_{50}) titers were 130.8 vs 83.9 for NVX-CoV2515 and NVX-CoV2373, respectively were geometric mean titre ratio (GMTR) of 1.6 (95% Confidence Interval [CI]: 1.33, 2.03) and seroresponse rates (SRRs) were 73.4% vs 50.9%, respectively (difference in SRR of 22.5% [95% CI: 10.3, 34.2]).

Descriptive analyses at Day 28 for Groups A and B also suggest NVX-CoV2515 produced more robust neutralization vs the Omicron BA.1 variant than NVX-CoV2373. Microneutralization GMTs were 160.0 vs 95.1, respectively, GMTR of 1.7 [95% CI: 0.64,

4.42]) and SRRs were 83.3% vs 75.0%, respectively (difference in SRR of 8.3% [95% CI: -26.2, 41.5]).

The secondary objective aiming to conclude non-inferiority of the bivalent vaccine with the strain-matched monovalent vaccine failed to meet endpoint criteria for success. Non-inferiority analysis of the bivalent vaccine vs NVX-CoV2515 using the Omicron BA.1 subvariant microneutralization assay at Day 14 found MN_{50} titers were 97.9 vs 130.8 for the bivalent vaccine and NVX-CoV2515, respectively (GMTR failed; 0.7 [95% CI: 0.59, 0.91]) and SRRs were 65.5% vs 73.4%, respectively (difference in SRR was -7.9% [95% CI: -19.6, 3.8]). At this point, no further statistical testing was conducted following the planned order of hypothesis testing.

Overall antibody responses at Day 28 were similar in participants previously vaccinated with 2 (Groups A and B) or 3 (Groups C, D, and E) doses of the Moderna and/or Pfizer-BioNTech prototype vaccines across the various assays and SARS-CoV-2 variants analysed. Day 28 Anti-S IgG antibody Geometric Mean ELISA Units (GMEUs) against the ancestral (Wuhan) strain in Group C, D, and E increased from baseline (Day 0) 2.1-fold for NVX-CoV2515 (40,833.4 ELISA Units per mL (EU/mL), 2.8-fold for NVX-CoV2373 (54,598.2 EU/mL), and 2.3-fold for the bivalent vaccine (41,070.0 EU/mL). SRRs were 16.4%, 30.0%, and 15.7%, respectively. In Group A and B, the same measures increased 6.0-fold for NVX-CoV2515 (38,039.0 EU/mL) and 7.9-fold for NVX-CoV2373 (55,989.9 EU/mL). SRRs were 66.7% and 75.0%, respectively. Comparison shows that similar peak titers were achieved although fold rises and SRRs were greater among participants who received fewer prior vaccinations. This finding was consistent among MN_{50} assay results for the Omicron BA.1, BA.5, and Ancestral strain as well.

Select antibody response data for select treatment groups was available through end of study (Day 240). Analysis of data to determine the durability of immune responses in participants with different vaccination histories found that responses remained elevated in participants previously vaccinated with 3 prior vaccinations (Groups C, D, and E), but not in those with 2 prior vaccinations (Groups A and B). Day 28 anti-S IgG antibody responses against the ancestral (Wuhan) S protein in Group C, D, and E (40,833.4 EU/mL, 54,598.2 EU/mL, and 41,070.0 EU/mL, respectively) were maintained through Day 240 (40,799.6 EU/mL, 48,341.9 EU/mL, and 42,378.5 EU/mL, respectively). However, similar Day 28 responses in Group A and B (38,039.0 EU/mL and 55,989.9 EU/mL, respectively) had decreased through Day 240 (18,147.2 EU/mL and 10,447.6 EU/mL, respectively).

Cell-mediated immune response data analysed at Day 14 (available for Groups C, D, and E) showed Geometric Mean Fold Rises (GMFRs) and triple and double cytokine expressing cell counts were similar within each treatment group following stimulation with either the BV2373 (Wuhan) or BV2601 (XBB.1.5) proteins. Nominally higher GMFRs and higher Day 14 cell counts for triple and double cytokine expressing cells were observed for participants in Group D relative to participants in Group C and Group E. Analyses at the individual cytokine level suggests there is a Th1-skewed response.

7.1.2.2 Safety Conclusions

The incidence of solicited local and systemic reactogenicity reported in this study was consistent with the reactogenicity seen in previous studies with NVX-CoV2373. Most solicited local injection site and systemic TEAEs were Grade 1 or Grade 2 in intensity, with Grade 3 local injection site TEAEs reported in less than 2% of participants and Grade 3 systemic TEAEs reported in ≤ 5% of participants. The median duration was 1 or 2 days for the solicited local injection site and systemic TEAEs. Frequencies of SAEs were low across the study, with 1 (1.6%), 2 (3.2%), 8 (2.8%), 4 (1.5%), and 4 (1.5%) participants experiencing events in Group A, B, C, D, and E, respectively; none were assessed as related to trial vaccine. AESIs of PIMMCs were reported in 5 participants overall, and all events were assessed as not related to trial vaccine. No fatal events occurred in this study. No events of myocarditis/pericarditis were reported across the 5 vaccine groups.

7.1.2.3 Overall Conclusions for Completed Study 2019nCoV-311 Part 1

- The co-primary endpoints of the study were achieved as the Omicron BA.1 subvariant vaccine NVX-CoV2515 induced a superior neutralizing antibody response in MN_{50} GMTs against the Omicron BA.1 subvariant virus along with a non-inferior SRR versus the prototype Novavax vaccine NVX-CoV2373 at Day 14 following booster administration in participants previously vaccinated with 3 doses of the Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines.
- Variant specific (NVX-CoV2515) and bivalent SARS-CoV-2 rS protein subunit vaccines demonstrated similar immunogenicity with no consistent benefits when compared to the prototype product (NVX-CoV2373) across several ancestral strain, Omicron BA.1, and Omicron BA.5 specific immunoassays.
- Overall antibody responses at Day 28 were similar in participants previously vaccinated with 2 (Groups A and B) or 3 (Groups C, D, and E) doses of the Moderna and/or Pfizer/BioNTech prototype vaccines across the various assays and SARS-CoV-2 variants analysed.
- The durability of immune responses through Day 240 was more robust in participants with 3 prior vaccinations (Groups C, D, and E) than those with 2 prior vaccinations (Groups A and B).
- NVX-CoV2515, NVX-CoV2373, and the bivalent vaccine were well-tolerated with an acceptable safety profile when used as heterologous booster doses in adult participants who had previously received 2 or 3 doses of prototype mRNA vaccines.

7.1.3 Study 2019nCoV-505

A Phase 2, Randomized, Observer-Blinded Study to Evaluate the Safety and Immunogenicity of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) with Matrix-M™ Adjuvant in People Living with HIV (PLWH)

Study 2019nCoV-505 was a Phase 2, randomized, observer-blinded study conducted in South Africa, evaluating the safety and immunogenicity of NVX-CoV2373 adjuvanted with Matrix-M adjuvant in people living with Human Immunodeficiency Virus (HIV) (PLWH) and HIV-negative adults who had not received any authorized SARS-CoV-2 vaccines. The investigational product was a monovalent SARS-CoV-2 prototype vaccine at a dose of 5 µg antigen adjuvanted with 50 µg Matrix-M (referred hereafter as NVX-CoV2373).

Approximately 280 PLWH, 18 to 65 years of age inclusive, were enrolled into three groups and stratified at presentation based on the level of control of HIV infection so that the distribution in all treatment groups reflected the population presented for study. People living with HIV were randomly assigned 1:1:1 to receive NVX-CoV2373 in either a two-dose regimen on Days 0 and 21 or Days 0 and 70 or a three-dose regimen on Days 0, 21, and 70. People living with HIV randomly assigned to treatment were stratified by level of control of HIV infection so as to distribute well-controlled and less-well-controlled participants approximately evenly among the 3 PLWH treatment groups.

Approximately 90 HIV-negative participants, 18 to 65 years of age inclusive, were randomly assigned 1:1 to receive NVX-CoV2373 in a two-dose regimen on Days 0 and 21 or Days 0 and 70.

The study operated under the hypothesis that an expanded interval between vaccinations or an additional immunizing exposure to vaccine will establish an optimal vaccine regimen that would mount an immune response in PLWH comparable to that seen in HIV-negative adults regardless of baseline serostatus. However, the hypothesis could not be evaluated because the majority of the study population (i.e., between 82.8% and 91.5% of participants depending on treatment group) was baseline seropositive.

7.1.3.1 Immunogenicity Conclusions

The immunogenicity objectives included a description of the amplitude, kinetics, and durability of immune response to NVX-CoV2373 in terms of Enzyme-linked Immunosorbent Assay (ELISA) units of serum anti-S Immunoglobulin G (IgG) antibodies, titers of neutralizing antibody, and titers of human Angiotensin Converting Enzyme 2 (hACE2) receptor binding inhibition activity assayed in a system using SARS-CoV-2 rS protein(s) at selected time points, stratified by baseline HIV status and in PLWH, stratified by level of control of HIV infection into well-controlled and less-well-controlled treatment groups. Exploratory objectives were designed to describe cellular immune response as measured by assays for interleukin-2 IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) to a

primary two-dose or three-dose regimen of NVX-CoV2373 in terms of antigen-specific clusters of differentiation 4 (CD4)+ T-cell responses.

For the ancestral (Wuhan) strain of SARS-CoV-2, a standard two-dose primary vaccination series of NVX-CoV2373 (vaccination on Days 0 and 21) induced comparable robust immune responses (anti-S IgG antibodies, hACE2 receptor binding inhibition, and neutralizing [MN50] antibodies) at Day 35 (i.e., 2 weeks post vaccination) in PLWH and HIV-negative South African participants ≥ 18 to ≤ 65 years of age. Compared with the other vaccine regimens evaluated in this study, the two-dose primary vaccination series was the optimal vaccine regimen for PLWH and HIV-negative participants. It is worth noting that in comparison with the values observed in the MN50, hACE2, and anti-S IgG assays the neutralizing antibody response based on the pseudovirus assay (ancestral Wuhan strain) for NVX-CoV2373 at Day 35 for PLWH after a standard two-dose primary vaccination series (Geometric Mean Titer [GMT] of 478.4 with a Geometric Mean Fold Rises [GMFR] of 10.2) was distinctly lower than that seen for HIV-negative participants who received the same treatment regimen (GMT of 4,484.2 with a GMFR of 16.4). This anomalous result may have been due to interference with the pseudovirus assay (as it is currently formulated) and caused by as yet unidentified factors specific to the serum samples obtained from PLWH. Relatively robust immune responses were also seen for PLWH on Day 84 after a two-dose primary vaccination series plus a third vaccination on Day 70 and these responses were higher than those seen at Day 84 after a standard two-dose primary vaccination series (indicating that a third vaccination in PLWH induced an effective booster response). By contrast, immune responses were generally lower post vaccination after a modified two-dose vaccination series (vaccination on Days 0 and 70) indicating that an expanded interval between vaccinations did not appear to provide an optimal vaccine regimen relative to either a standard two-dose primary vaccination series or a standard two-dose vaccination series plus a third vaccination. Immune responses for PLWH with well-controlled and less-well-controlled HIV infection were comparable and equally robust and followed the same pattern of responses as those seen for the population as a whole. Immune responses for the Omicron BA.1 and BA.5 subvariants followed the same pattern as that seen for the ancestral Wuhan strain but were relatively modest.

In terms of cell mediated immunity for the ancestral Wuhan strain, the greatest (i.e., robust) response was seen for TNF-α+ CD4+ T cells followed by interleukin-2+ CD4+ T cells, Two+ Thl CD4+ T cells, and interferon-γ + CD4+ T cells which showed a more modest response. Cell mediated immunity responses for the Omicron BA.5 and BQ1.1 subvariants exhibited the same pattern as that seen for the ancestral Wuhan strain but were relatively modest.

7.1.3.2 Safety Conclusions

Safety objectives included an assessment of overall safety after initial vaccination for all unsolicited Treatment Emergent AEs (TEAEs), Medically Attended AEs (MAAEs), MAAE attributed to vaccine, Adverse Events of Special Interest (AESI), or SAEs and a description of

the solicited short-term reactogenicity (by toxicity grade) by TEAE profile in PLWH and HIV-negative adult participants and in PLWH stratified by level of control of HIV infection, into well-controlled and less-well-controlled treatment groups. The majority of participants across all treatment groups overall did not experience solicited local or systemic TEAEs following vaccination. Few participants reported grade 3 (i.e., severe) solicited local or systemic events (ranges of 1.2 to 2.4% and 1.8 to 4.9%, respectively). Pain and tenderness were the most frequently reported solicited local TEAEs and headache and muscle pain were the most frequently reported solicited systemic TEAEs after each vaccination across all subsets of participants. Median durations varied between 3.0 and 6.0 days and 2.0 and 4.0 days for solicited local and systemic TEAEs, respectively, depending on category of individual solicited local or systemic TEAE, level of HIV infection control, and HIV status.

The frequencies of participants with unsolicited serious TEAEs were relatively low and similar across treatment groups (range from 1.9% to 4.1%). No unsolicited serious TEAEs were assessed as related to trial vaccine. One SAE leading to death was reported, assessed as not related to trial vaccine. No AESI: PIMMC, AESI: COVID-19, or AESI: myocarditis/pericarditis were reported in this study.

7.1.3.3 Overall Conclusions for Completed Study 2019nCoV-505

- A standard two-dose primary vaccination series with NVX-CoV2373 (administered at Days 0 and 21) in PLWH induced a robust immune response comparable to that seen for HIV-negative participants who received the same treatment regimen.
- A standard two-dose primary vaccination series plus a third dose of NVX-CoV2373 (administered at Day 70) in PLWH induced a relatively modest immune response compared with that seen immediately after administration of a standard two-dose primary vaccination series.
- A modified two-dose vaccination series with NVX-CoV2373 (administered at Days 0 and 70) induced a suboptimal immune response in PLWH and HIV-negative participants.
- The pattern of immune responses in PLWH with well-controlled and less-well-controlled HIV infection were comparable to those seen for the population as a whole.
- NVX-CoV2373 was well tolerated with a favourable safety profile.

7.2 Ongoing Clinical Trials

As of the DLP for this PBRER (19-Jun-2024), 7 clinical trials (which includes two multi-part clinical trials) were ongoing: 2019nCoV-205, 2019nCoV-301 (Adolescent Main and Adolescent Booster), 2019nCoV-311 Part 1, 2019nCoV-312, 2019nCoV-313 (Parts 1 and 2), 2019nCoV-314, and 2019nCoV-503.

During the reporting interval for this PBRER, an interim analysis became available for one ongoing clinical trial, 2019nCoV-313 Part 1. A brief summary of the clinically important

safety and immunogenicity results obtained from the interim CSR for 2019nCoV-313 Part 1 is summarized below. No new safety information emerged from this ongoing clinical trial.

7.2.1 Study 2019nCoV-205

Study 2019nCoV-205 is an ongoing Phase 2/3 randomized, double-blind study conducted in the US, to evaluate the safety and immunogenicity of different booster dose levels of monovalent SARS-CoV-2 rS vaccines in adults ≥ 50 years previously vaccinated with COVID-19 mRNA vaccines. No interim analysis for this study was conducted during this PBRER reporting interval.

7.2.2 Study 2019nCoV-301 Adolescent Main and Adolescent Booster

Study 2019nCoV-301 is a 4-part Phase 3, multinational, multicenter, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant (also referred to as NVX-CoV2373) in adult participants ≥ 18 years of age in the US and Mexico (Adult Main Study) with a Pediatric Expansion in adolescents 12 to < 18 years of age and a Booster Amendment (Adult and Pediatric).

As of the DLP, only the Adolescent Main and the Adolescent Booster were ongoing. No interim analyses were planned or conducted for the remaining two parts, namely the Adolescent Main and the Adolescent Booster.

7.2.3 Study 2019nCoV-311 Part 2

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

Study 2019nCoV-311 Part 2 is an ongoing Phase 3, randomized, observer-blinded study evaluating the immunogenicity and safety of 2 booster vaccinations of the prototype Novavax vaccine (NVX-CoV2373), the Omicron BA.5 subvariant vaccine (NVX-CoV2540), and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) in previously vaccinated adults ≥ 18 years of age who previously received ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously. The following information was obtained from the interim CSR dated 17-Apr-2024 for Study 2019nCoV-311 Part 2.

7.2.3.1 Immunogenicity Conclusions

7.2.3.1.1 Neutralizing Antibody Responses

Neutralizing Antibody Responses Against the Omicron BA.5 Subvariant Pseudovirus

Neutralising Antibodies (NAbs) (ID50) against the Omicron BA.5 subvariant pseudovirus, the ancestral (Wuhan) pseudovirus, and the Omicron XBB.1.5 subvariant pseudovirus were assessed at Day 0 (baseline), Day 14, Day 28, Day 90, Day104, and Day 118 using a validated pseudovirus neutralisation assay (Novavax Clinical Immunology).

The co-primary endpoint of superiority was achieved as the bivalent vaccine induced a superior NAb response in ID50 adjusted GMT versus NVX-CoV2373 in regard to the induction of NAbs against the Omicron BA.5 subvariant pseudovirus (1,017.8 vs 515.1, respectively) at Day 28, with a GMTR of 2.0 (95% CI: 1.69, 2.33) and a lower boundary of the two-sided 95% CI > 1 (1.69). The co-primary endpoint of non-inferiority was also achieved as the bivalent vaccine induced a non-inferior SRR against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 (39.8% vs 12.3%, respectively) at Day 28, with a difference in SRRs of 27.5% (95% CI: 19.8, 35.0) and a lower boundary of the two-sided 95% CI > -5% (19.8%). The co-primary endpoint of non-inferiority was also achieved as the bivalent vaccine induced a non-inferior response in ID50 adjusted GMT versus NVX-CoV2373 in regard to the induction of NAbs against the ancestral (Wuhan) pseudovirus (2,211.1 vs 2,205.6, respectively) at Day 28, with a GMTR of 1.0 (95% CI: 0.84, 1.20) and a lower boundary of the two-sided 95% CI > 0.67 (0.84).

NAb responses against the Omicron BA.5 subvariant pseudovirus and the Omicron XBB.1.5 pseudovirus were more robust at all time points after both booster vaccinations with the bivalent vaccine versus NVX-CoV2373 while NAb responses against the ancestral (Wuhan) pseudovirus were similar for the bivalent vaccine versus NVX-CoV2373 vaccine.

NAb responses against the Omicron BA.5 subvariant pseudovirus and Omicron XBB.1.5 subvariant pseudovirus were higher for younger (18 to 54 years) versus older (≥ 55 years) participants at all time points after both booster vaccinations with either the bivalent vaccine or NVX-CoV2373 while NAb responses against the ancestral (Wuhan) pseudovirus were similar for younger versus older participants both for the bivalent vaccine and NVX-CoV2373.

NAb responses for the bivalent vaccine and NVX-CoV2373 were also compared to those seen for NVX-CoV2540. The magnitude of the NAb response for NVX-CoV2540 was generally higher in terms of GMT (ID50) and GMFR versus NVX-CoV2373 but similar to that seen for the bivalent vaccine. It is interesting to note that the extent to which responses were increased with NVX-CoV2540 and the bivalent vaccine versus NVX-CoV2373 were similar, suggesting that NVX-CoV2540 was the main active component in the bivalent vaccine. In addition, in an exploratory analysis, NVX-CoV2540 induced a superior response in ID50 adjusted GMT (Monogram Biosciences) versus NVX-CoV2373 in regard to the induction of NAbs against

the Omicron BA.4/5 subvariant pseudovirus or Omicron XBB.1.5 subvariant pseudovirus with GMTRs of 2.5 (95% CI: 2.16, 2.95) and 3.2 (95% CI: 2.70, 3.84), respectively.

7.2.3.2 Safety Conclusions

NVX-CoV2540, NVX-CoV2373, and NVX-CoV2373 + NVX-CoV2540 were well tolerated with an acceptable safety profile after initial and second booster vaccination in adult participants who had previously received ≥ 3 vaccinations of Moderna and/or Pfizer-BioNTech prototype mRNA COVID-19 vaccines.

Safety objectives included an assessment of overall safety after initial and second vaccinations for all unsolicited AEs, MAAEs, related MAAEs (i.e., attributed to vaccine), AESI, or SAEs and a description of the solicited short-term reactogenicity (by toxicity grade) by AE.

Solicited AEs after initial and second booster vaccination were similar between the 3 study vaccine groups (overall range between 71.8% to 78.8%). Most solicited AEs were mild or moderate in severity, with median days of onset between Day 1 and Day 2 and median durations between 2.0 and 3.0 days. Few participants reported grade 3 solicited local or systemic AEs following initial vaccination (≤ 1.6% and ≤ 4.0%, respectively) or second vaccination (≤ 1.7% and ≤ 5.3%). One (0.4%) participant reported a grade 4 solicited systemic AE (fatigue/malaise).

Few participants had SAEs with a range of 0.4% to 2.0% between study vaccine groups; 1 (0.4%) participant had a related SAE of IVth nerve paralysis in the NVX-CoV2540 group. No participant had an SAE with an outcome of death in this study. AESI: PIMMCs were relatively low (frequency [≤ 0.8%] and no AESIs related to COVID-19 were reported. No events of myocarditis/pericarditis were reported throughout the study.

7.2.3.3 Overall Conclusions for Part 2 of Ongoing Study 2019nCoV-311

The overall conclusions of the ad-hoc Day 189 interim analysis are:

- The bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induced superior antibody responses following both vaccinations compared to the antibody responses induced by NVX-CoV2373.
- NVX-CoV2540 induced superior antibody responses compared with NVX-CoV2373.
- NVX-CoV2540, NVX-CoV2373, and the bivalent vaccine were well tolerated with an acceptable safety profile when used as heterologous booster doses in adult participants who had previously received ≥ 3 doses of mRNA COVID-19 vaccines.

7.2.4 Study 2019nCoV-312

Study 2019nCoV-312 is a Phase 3 study to evaluate the immunogenicity and safety of NVX COVID-19 vaccine(s) as second or subsequent boosters after mRNA vaccines in individuals

18 to 49. No interim analysis for this study was planned or conducted during the reporting interval for this PBRER.

7.2.5 Study 2019nCoV-313 Parts 1 and 2

A 2-Part Phase 2/3 Open-Label Study to Evaluate the Safety and Immunogenicity of an XBB.1.5 (Omicron Subvariant) SARS-CoV-2 rS Vaccine Booster Dose in Previously mRNA COVID-19 Vaccinated and Baseline SARS-CoV-2 Seropositive COVID-19 Vaccine Naïve Participants

Study 2019nCoV-313 is an ongoing single-arm study to evaluate the safety and immunogenicity of a booster dose of NVX-CoV2601 in previously messenger ribonucleic acid (mRNA) COVID-19 vaccinated adult participants ≥ 18 years of age (Part 1) and in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants ≥ 18 years of age (Part 2) in the US and its territories (Protocol 2019nCoV-313 [v3.0, dated 27-Nov-2023] and Statistical Analysis Plan [v1.0, dated 21 June 2023]). In Part 1 and Part 2 of this study, participants received a booster vaccination on Day 0 and will be followed for immunogenicity and safety data collection through Day 180 with interim analyses planned on Day 28.

During the reporting interval for this PBRER, an interim CSR for Part 1 of this study became available and it is summarised below. However, no interim analysis for Part 2 of this study was planned or conducted during the reporting interval for this PBRER.

The following information was obtained from the interim CSR for Study 2019nCoV-313 Part 1, dated 29-Mar-2024, which presented results of a planned Day 28 interim analysis as of the data cutoff date of 16-Oct-2023 and data extraction date of 17-Jan-2024.

Part 1 of Study 2019nCoV-313 was initiated on 07-Sep-2023 (first participant screened) and completed enrolment on 08-Sep-2023. The co-primary objectives in Part 1 were 1) to determine if NVX-CoV2601 booster induced superior antibody responses to the Omicron XBB.1.5 subvariant compared to the antibody responses of a historical control of NVXCoV2373 and 2) to determine if NVX-CoV2601 booster induced non-inferior SRRs compared to SRRs of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations.

The historical control group of NVX-CoV2373 booster used in Part 1 of the study was derived from Group G in Part 2 of Study 2019nCoV-311, an ongoing Phase 3, randomized, observer-blinded study evaluating the safety and immunogenicity of the Omicron BA.5 subvariant vaccine (NVX-CoV2540) in medically stable male or non-pregnant female participants ≥ 18 years of age who had previously received ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days prior to study vaccination; this study was conducted in Australia and initiated on 22- Mar-2023. Of the 766 participants randomized in Part 2 of Study 2019nCoV-311, 252 were randomly assigned to Group G with 251 receiving a booster dose of NVX-CoV2373 on Day 0. An interim analysis of

immunogenicity and safety data was performed on Day 28, with results presented in 2019nCoV-311 Part 2 Interim Analysis (v1.0, dated 17-Jul-2023).

The results of the planned Day 28 interim analysis comprise all primary and secondary immunogenicity endpoints at Day 28 and safety analysis through the data cutoff date. Exploratory immunogenicity analyses, as well as long-term immunogenicity and safety will be presented in a separate report. Results of the planned Day 28 interim analysis of Part 2 of Study 2019nCoV-313 will also be presented in a separate report.

A total of 332 participants were enrolled in the study at 30 sites in the US and its territories, with 329 (99.1%) in follow up. Data from 1 site (Site US263) were not used in the immunogenicity analysis but were included in the safety analysis due to data compliance issues.

7.2.5.1 Immunogenicity Conclusions

Both co-primary endpoints were achieved in Part 1 of Study 2019nCoV-313, with the first co-primary endpoint demonstrating the superiority of the NVX-CoV2601 booster compared to the historical control NVX-CoV2373 booster against the Omicron XBB.1.5 subvariant pseudovirus (905.9 vs 156.6, respectively) as measured by the between-group GMTRs (5.8 [95% CI: 4.85, 6.91]) of ID50 GMTs (adjusted) at Day 28 as the lower limit of the 95% CI for the difference between the 2 vaccines exceeded 1 (4.85). The second co-primary endpoint demonstrated non-inferiority of the NVX-CoV2601 booster compared to the historical control NVX-CoV2373 booster for the difference in SRRs at Day 28 when the lower limit of the 95% CI for the difference between the two booster vaccines exceeded -10% (50.5%). The SRRs of NVX-CoV2601 and the historical control NVX-CoV2373 were 64.3% (95% CI: 58.6, 69.6) versus 7.0% (95%CI: 4.1, 11.2), respectively, at Day 28. The difference in SRRs was 57.2% (95% CI: 50.5, 63.2).

Subgroup analyses by age group (18 to 54 years or ≥ 55 years), previous COVID-19 mRNA vaccine regimen (Pfizer-BioNTech, Moderna, or Moderna or Pfizer-BioNTech), and baseline anti-N status (anti-N positive or anti-N negative) continued to show that NVX-CoV2601 booster elicited strong adjusted GMT (ID50) responses against the Omicron XBB.1.5 subvariant virus compared to the historical control NVX-CoV2373 booster at Day 28.

As a secondary endpoint, GMFRs at Day 28 following booster vaccination with NVX-CoV2601 were statistically significantly higher ($p < 0.001$) versus baseline for all participants; participants 18 to 54 years of age or ≥ 55 years of age; participants who previously received Pfizer-BioNTech, Moderna, or Moderna plus Pfizer-BioNTech COVID-19 mRNA vaccines; participants who previously received COVID-19 mRNA vaccine for Wuhan only, Omicron BA.4/BA.5 bivalent, or Wuhan plus Omicron BA.4/BA.5 bivalent; and in SARS-CoV-2 anti N positive or SARS-CoV-2 anti-N negative NVX-CoV2601 participants.

As a secondary endpoint, the Omicron XBB.1.5 subvariant vaccine NVX-CoV2601 induced a stronger anti-S IgG antibody response against Omicron XBB.1.5 subvariant S protein than the

historical control prototype Novavax Vaccine NVX-CoV2373 at Day 28, with adjusted GMEUs of 79761.5 versus 44325.4 EU/mL, respectively. GMFRs referencing Day 0 were 3.5 and 2.1, respectively, for the NVX-CoV2601 and historical control NVX-CoV2373 groups. SRRs were also higher in NVX-CoV2601 recipients than historical control NVX-CoV2373 recipients (39.7% vs 15.4%, respectively).

7.2.5.2 Safety Conclusions

The incidence of solicited local injection site and systemic reactogenicity reported in this study was consistent with the reactogenicity seen in previous studies with NVX-CoV2373. Solicited local injection site and systemic TEAEs were reported in 189 (56.9%) and 158 (47.6%) participants, respectively, with most participants reporting grade 1 or grade 2 events. Few participants reported grade 3 events, and no participant reported grade 4 events. Higher frequencies of solicited local injection site and systemic TEAEs were reported in participants 18 to 54 years of age (64.2% and 51.7%, respectively) than in participants ≥ 55 years of age (48.7% and 42.9%, respectively). Pain/tenderness, fatigue/malaise, muscle pain, and headache were the most frequent (incidence > 20%). Median days of onset were Day 1 and Day 2 for most events; Day 3 for redness and joint pain; and Day 4 for fever and nausea/vomiting. Median durations were 1 to 2 days for all events except fever, with a median duration of 3.5 days for fever.

There were no deaths, treatment-related SAEs, AESIs (potential immune mediated medical condition or COVID-19 related), and TEAEs of myocarditis/pericarditis reported. Collectively, these data demonstrated no obvious change in the safety profile of SARS-CoV-2 rS protein subunit vaccines with XBB.1.5 strain change.

7.2.5.3 Overall Conclusions for Ongoing Study 2019nCoV-313 Part 1

The overall conclusions of this interim analysis are:

- The co-primary endpoints of the study were achieved, as the Omicron XBB.1.5 subvariant vaccine NVX-CoV2601 induced a superior neutralizing antibody response in adjusted GMT (ID50) against the Omicron XBB.1.5 subvariant virus along with a non-inferior SRR versus the prototype Novavax vaccine NVX-CoV2373 at Day 28 following booster administration in participants previously vaccinated with ≥ 3 doses of prototype or bivalent COVID-19 mRNA vaccines.
- NVX-CoV2601 was well tolerated, with an acceptable safety profile when used as heterologous booster doses in adult participants who had previously received prototype monovalent and/or BA.4/5 containing bivalent mRNA vaccines.

7.2.6 Study 2019nCoV-314

Study 2019nCoV-314 is a Phase 3, randomized, double-blinded study to evaluate the safety and immunogenicity of omicron subvariant and bivalent SARS-CoV-2 rS vaccines in

adolescents previously vaccinated with mRNA COVID-19 vaccines. No interim analysis for this study was planned or conducted during the reporting interval for this PBRER.

7.2.7 Study 2019nCoV-503

Study 2019nCoV-503 is a Phase 2/3 age de-escalating study to evaluate the safety and immunogenicity of SARS-CoV-2 rS protein vaccine with Matrix-M adjuvant in children 6 months to < 12 years of age. No interim analysis for this study was planned or conducted during the reporting interval for this PBRER.

7.3 Long-Term Follow-Up

Most NVX-sponsored clinical trials collect up to 1 year of follow-up data for enrolled participants, except Study 2019nCoV-301 which collects up to 2 years of follow-up data. No new safety information became available from long-term follow-up in NVX-sponsored clinical trials, as of the DLP.

7.4 Other Therapeutic Use of Medicinal Product

No programs involving other therapeutic uses of Nuvaxovid or Nuvaxovid XBB.1.5 were ongoing during the reporting interval.

7.5 New Safety Data Related to Fixed Combination Therapies

During the reporting interval, there was 1 completed NVX-sponsored clinical trial involving CIC vaccine, Phase 2 study, 2019nCoV-CIC-E-201, and there were no significant safety findings from the study as of DLP.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting interval, 3 NVX-sponsored Post-Authorisation Safety Studies (PASS) and 4 NVX-sponsored Post-Authorisation Efficacy Studies (PAES) were ongoing and 2 NVX-sponsored PAES studies were completed. There was also 1 collaborative research PAES study that was ongoing during the reporting interval. No new findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported from any non-interventional studies.

Appendix 9 provides further details of the ongoing/completed non-interventional studies from the reporting interval.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

During the reporting interval, there were 5 ongoing and 4 completed investigator-initiated studies, and 1 completed license partner-sponsored study (briefly summarized below, due to

its relevance to potential waning immunity). No significant safety findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported.

Appendix 8, Table 36 summarises studies managed by license partners and Table 37 summarises details regarding ongoing and completed investigator-initiated studies.

In Study TAK-019-3001, Extension Part, 129 participants received a second booster vaccination of TAK-019. The second booster Dose of TAK-019 as a heterologous vaccine elicited rapid and robust immune responses for serum IgG antibody and serum neutralizing antibody, which addressed waning immunity after the first booster Dose of TAK-019 following the primary series of Comirnaty injection. The second booster Dose of TAK-019 as a heterologous vaccine was well-tolerated with no new safety concerns and had an acceptable safety profile through 1 year after the second booster vaccination.

9.2 Medication Errors

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for Medication (vaccination) errors (refer to Appendix 14).

9.2.1 Results and Discussion

Cases with Nuvaxovid:

Ten initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 268 ICSRs were retrieved (103 males, 135 females, 30 individuals of unspecified sex, age range 4 – 94 years, when reported), which contained 333 AEs. The most frequently reported PTs (n≥20) were Expired product administered (n=51), Incomplete course of vaccination (n=36), Inappropriate schedule of product administration (n=33), Interchange of vaccine products (n=30), Vaccination error (n=23), Product administration error (n=21) and Product administered to patient of inappropriate age (n=20). Of the 333 AEs reported, 6 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 5 medically significant (based on medical judgement or serious by convention, meeting IME criteria), and 1 death.

Cases with Nuvaxovid XBB.1.5:

Forty initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 83 ICSRs were retrieved (44 males, 35 females, 4 individuals of unspecified sex, age range 8 – 89 years, when reported). These 83 cumulative ICSRs contained 123 non-serious AEs and no serious AEs. The most frequently reported PTs (n≥10) were Product storage error (n=38), Expired product administered (n=37) and Product administration error (n=28).

During the current reporting interval, a disproportionate number of reports (n=41 ICSRs) falling under the MedDRA high level term (HLT) Product administration errors and issues was detected with a majority of ICSRs reporting events of Expired product administered (n=28). All reports were non-serious. No associated quality complaints were received and there was no indication of product label or instructions for use concerns. Given that no trend has been detected beyond this isolated event of disproportionate reporting, no signal requiring validation was generated.

9.2.2 Conclusion

One observation of disproportionate reporting related to Expired product administered was identified during the reporting interval. Following case-level review, no signal requiring validation was identified. Medication (vaccination) errors, including reports of Expired product administered will continue to be monitored through routine pharmacovigilance activities.

10 NON-CLINICAL DATA

During the reporting interval, there were 8 completed and 15 ongoing non-clinical studies for SARS-CoV-2 rS. There were no significant safety findings from non-clinical studies that impacted the benefit-risk profile of SARS-CoV-2 rS.

Table 13 provides a summary of non-clinical studies for SARS-CoV-2 rS that were either ongoing or completed during the reporting interval.

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
Completed Studies				
24#367 Pilot study: Dose-finding study for AF647-labeled SARS-CoV-2 rS antigen. (complete)	SVA Swedish national Veterinary Institute, In life, Novavax, Flowcytometry (Non-GLP)	BALB/c mice (1-3 mice/group, females, total 13 mice)	Mice were immunized intramuscularly in the right quadriceps femoris (thigh) muscle. Twenty-four hours (±15 min) after immunization, the mice are euthanized and the muscle, draining iliac lymph node, and spleen are harvested. Analysed by flowcytometry. Matrix-M, 5 µg, 1 mouse. 5 µg Matrix-M with BODIPY labelled Matrix-A (10%) + 0.33 µg AF647-labeled SARS-CoV-2 rS, 3 mice. 5 µg Matrix-M with BODIPY labelled Matrix-A (10%) + 1.1 µg AF647-labeled SARS-CoV-2 rS, 3 mice. 5 µg Matrix-M with BODIPY labelled Matrix-A (10%) + 3.3 µg AF647-labeled SARS-CoV-2 rS, 3 mice. 5 µg Matrix-M with BODIPY labelled Matrix-A (10%) + 10 µg AF647-labeled SARS-CoV-2 rS, 3 mice.	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-115 Long-term immunogenicity & protective efficacy in rhesus macaques (complete)	Karolinska Inst	Rhesus Macaques (N=21 Total)	Group 1 and 2 5 µg Prototype BV2373 + 50 µg Matrix-M1 - Week 0 and 4 Booster 5 µg P.1 BV2443 + 50 µg Matrix-M1- Week 35 Challenge WA-1/2020 (group 1), P.1 (group 2)- Week 66 Group 3 and 4 5 µg Prototype BV2373 or P1 BV2443 + 50 µg Matrix-M1 - Week 35 and 39 Challenge P.1 (group 2) - Week 66 Booster with Prototype + BA.5 rS (2.5 µg each rS + 50 µg Matrix-M1)- Week 108 Challenge with XBB.1.5- Week 135	No new safety findings
702-134 Immunogenicity of Monovalent and Bivalent BA.5 Booster in Baboons- One Year Study (complete)	OUHSC (in-life) Novavax (immune response) Non-GLP	Olive baboons (n = 6/group)	Primary Series administered IM Day 0 and 28 5 µg Prototype BV2373 or Omicron BA.1 BV2515 + 50 µg Matrix-M1 Booster administered IM on Day 150 5 µg Omicron BA.5 or Prototype + BA.5 + 50 µg Matrix-M1	No new safety findings
702-149 Evaluation of 6 Month Booster Immunization with Prototype, Omicron BA.1, and Bivalent Vaccines in Rhesus (complete)	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Primary Series administered IM Day 0 and 21 5µg SARS-CoV-2 rS BV2373 + 5 µg Matrix-M1 5µg SARS-CoV-2 rS Delta + 5 µg Matrix-M1 Booster administered IM on Day 182 5 µg Prototype, BA.1, or Prototype + BA.1 + 50 µg Matrix-M1	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-191 Immunogenicity Study 1 in Mice to support Variant Change (complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	Primary Series Day 0 and 14 1 µg prototype with 5 µg Matrix-M 1 µg (total rS) bivalent prototype + BA.5 with 5 µg Matrix-M 1 month boost with monovalent rS Day 47 1 µg prototype, BA.5, XBB.1.5, BQ.1.1, CH1.1, XBB.1.16 with 5 µg Matrix-M 1 month boost with bivalent rS Day 47 1 µg Prototype+BA.5, Prototype+XBB.1.5, Prototype+XBB.1.16, Prototype+BQ.1.1 with 5 µg Matrix-M	No new safety findings
702-208 SARS-CoV-2 DP Potency in mice (complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n=10/group)	Immunization Day 0 and 14 by IM 2-fold serial dilutions of Prototype DP and XBB.1.5 DP (0.5, 0.25, 0.125, 0.0625, 0.0313, 0.0156, 0.0078, 0.0039µg)	No new safety findings
702-212 In-Vivo Potency of OOS XBB.1.5 DPs in mice (complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n=10/group)	Immunization Day 0 and 14 by IM 0.5, 0.05, 0.005 µg XBB.1.5 DP lots: 5683MF001 ~9m aged 5683MF003 ~9m aged MD20230068 ~2.5m aged 5684MF001 ~2m aged	No new safety findings
702-213 Omicron XBB.1.5 and JN.1 DPs in-vivo Potency in mice (complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n=10/group)	Immunization Day 0 and 14 by IM 3-fold serial dilutions of Prototype, XBB.1.5, and JN.1 DPs (0.5, 0.167, 0.056, 0.019, 0.006, 0.002 µg)	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
Ongoing Studies				
24#370 Immunogenicity in WT and NLRP3 KO mice (ongoing)	SVA Swedish national Veterinary Institute, In life, Novavax, Immunogenicity (Non-GLP)	C57BL/6 mice or Nlrp3 deficient mice (B6.129S6-Nlrp3^{tm1Bhk}/J) (10 mice/group, females, total 80 mice)	0.1 µg SARS-CoV-2 rS Prototype BV2373 unadjuvanted control or adjuvanted with 5 µg Matrix-M adjuvant, Matrix-A, or Matrix-C adjuvant components Administered S.C. at the base of the tail on Days 0 and 21	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-173 Evaluation of Prototype and Omicron Variants in Rhesus (ongoing)	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Day 0 and 21 Vaccination (IM) (Groups 1-4)-complete 5µg SARS-CoV-2 rS BV2373 + 50 µg Matrix-M1 5µg SARS-CoV-2 rS Omicron BA.5 + 50 µg Matrix-M1 Bivalent 5µg (2.5 µg each rS) SARS-CoV-2 rS (Prototype BV2373 + Omicron BA.5) + 50 µg Matrix-M1 Booster Day 246 ~8 month (Groups 1-4)-complete 5 µg BQ.1.1 or XBB.1.5 with 50 µg Matrix-M1 Primary Series Day 246 and 267 (Groups 5 and 6) 5 µg XBB.15 with 50 µg Matrix-M 1st Booster (Groups 5 and 6) Day 456 Group 5: 5 µg XBB.1.5 with 50 µg Matrix-M (IM) Group 6: 25 µg XBB.1.5 with 50 µg Matrix-M (IN) 2nd Booster Day 604 (Groups 5 and 6) 5 µg JN.1 rS with 50 µg Matrix-M 5 µg JN.1.11.1 rS with 50 µg Matrix-M	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-181 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron BF.7, BQ.1, and BQ.1.1 Variants in Mice. (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	0.1 and 1 µg Prototype BV2373, Omicron BF.7, BQ.1, and BQ.1.1 + 5 µg Matrix-M Administered IM on days 0 and 14	No new safety findings
702-185 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron XBB, XBB.1, and BN.1 Variants in Mice. (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	0.1 and 1 µg Prototype BV2373, Omicron XBB, XBB.1, and BN.1 + 5 µg Matrix-M Administered IM on days 0 and 14	No new safety findings
702-194 Immunogenicity Study 2 in Mice to support Variant Change (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	Primary Series Day 0 and 14 1 µg BQ.1.1, XBB.1.5, BQ.1.1+XBB.1.5, or BA.5+XBB.1.5 with 5 µg Matrix-M 1 month boost Day 44 0.5 or 1 µg XBB.1.5 with 5 µg Matrix-M 0.5 or 1 µg XBB.1.16 with 5 µg Matrix-M	No new safety findings
702-196 Immunogenicity of SARS-CoV-2 rS Prototype and Omicron Variants BA.5, XBB.1.5, XBB.2.3 and XBB.1.16 in mice (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10-15/group)	Immunization Day 0 and 14 1 µg Prototype, BA.5, XBB.1.5, XBB.1.16 with 5 µg Matrix-M Booster (3 month) 1 µg XBB.1.5 with 5 µg Matrix-M	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-200 Immunogenicity of Intranasal booster with Omicron XBB.1.5 rS-PACE in Mice. (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 9-10/group)	Immunization Day 0 and 14 (Primary series) by IM 1 µg Prototype rS + 1 µg BA.5 rS with 5 µg Matrix-M Booster Day 48 (1 month) 1 µg XBB.1.5 rS ± 5 µg Matrix-M IM 1 µg XBB.1.5 rS ± 5 µg Matrix-M IN 1 µg XBB.1.5 in Xanadu Formulations A, B, C ± 5 µg Matrix-M IN	No new safety findings
702-202 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron XBB1.5, XBB.1.16.6, and EG.5.1 Variants in Mice. (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-15/group)	Immunization Day 0 and 14 by IM 1 µg XBB.1.5, XBB.1.16.6, or EG.5.1 rS with 5 µg Matrix-M	No new safety findings
702-203 Immunogenicity of SARS-CoV-2 rS Omicron XBB.1.5, BA.2.86, and FL.1.5.1 Variants in Mice- booster study (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 20/group)	Immunization Day 0 and 14 by IM 1 µg XBB.1.5, BA.2.86, or FL.1.5.1 rS with 5 µg Matrix-M Booster (3 month) Day 105 1 µg XBB.1.5 rS with 5 µg Matrix-M 1 µg JN.1 rS with 5 µg Matrix-M	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-204 Immunogenicity of Intranasal booster with Omicron XBB.1.5 rS in Mice. (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 5-8/group)	Immunization Day 0 and 14 (Primary series) by IN/IM 1 µg Prototype rS + 1 µg BA.5 rS with 5 µg Matrix-M (IM/IN) 1 µg XBB.1.5 rS with 5 µg Matrix-M (IM/IN) 5 µg Prototype rS + 5 µg BA.5 rS with 5 µg Matrix-M (IN) 5 µg XBB.1.5 rS with 5 µg Matrix-M (IN) Booster - 1 month 1 µg XBB.1.5 rS + 5 µg Matrix-M (IM/IN) 5 µg XBB.1.5 rS + 5 µg Matrix-M (IN)	No new safety findings
702-207 Booster Study in Mice Primed with Monovalent XBB.1.5 rS, Trivalent Prototype+BA.5+XBB.1.5 rS, and HV.1 rS (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 20/group)	Immunization Day 0 and 14 (Primary series) 1 µg XBB.1.5 rS, JN.1 rS, or HV.1 rS with 5 µg Matrix-M 1 µg each Prototype rS+BA.5 rS+XBB.1.5 rS with 5 µg Matrix-M Booster - 2 month 1 µg XBB.1.5 rS or JN.1 rS with 5 µg Matrix-M Booster – 3.5 month 1 µg JN.1 rS or JN.1.11.1 rS with 5 µg Matrix-M	No new safety findings
702-210 Immunogenicity Study with New Emerging variants in mice (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 20/group)	Immunization Day 0 and 14 (Primary series only) 1 µg XBB.1.5 rS, JN.1 rS, HV.1, or HK.3 rS with 5 µg Matrix-M	No new safety findings

Table 13: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Study Number & Description (Status)	Testing Facility (GLP Status)	Animals (N)	Study Design (Treatment Groups/ Administration/Endpoints)	Key Safety Conclusions
702-214 Immunogenicity of XBB.1.5 and JN.1 rS by intranasal administration in mice (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-6/group)	Immunization Day 0 and 14 by IM/IN 1 or 5 µg XBB.1.5 rS with 5 µg Matrix-M (IN) 1 or 5 µg JN.1 rS with 5 µg Matrix-M (IN) 1 µg JN.1 rS with 5 µg Matrix-M (IM)	No new safety findings
702-216 Immunogenicity of XBB.1.5, JN.1, and JN.1.11.1 rS in mice (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 6-10/group)	Immunization Day 0 and 14 by IM 1 µg XBB.1.5 rS with 5 µg Matrix-M 1 µg JN.1 rS with 5 µg Matrix-M 1 µg JN.1.11.1 rS with 5 µg Matrix-M	No new safety findings
702-219 Immunogenicity of JN.1, JN.1.13.1, and KP.2 rS in mice (in-life complete)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-10/group)	Immunization Day 0 and 14 by IM 1 µg JN.1 rS with 5 µg Matrix-M 1 µg JN.1.13.1 rS with 5 µg Matrix-M 1 µg KP.2 rS with 5 µg Matrix-M	No new safety findings

BALB - Albino, laboratory-bred strain of the house mouse, BODIPY - Boron-Dipyrromethane, C57BL/6 - inbred strain of laboratory mouse. GLP - Good Laboratory Practices, Nlrp3- NLR family pyrin domain containing 3, S.C-subcutaneous, SVA-Swedish national veterinary institute, IM – Intramuscular, IN – Intranasal, NLS – Noble Life Sciences, OUHSC - University of Oklahoma Health Sciences Center , WT – wilde type, NLRP3 KO - NLR family pyrin domain containing 3 knockout, PACE –Poly(amine-*co*-ester) , DP – Drug Product

11 LITERATURE

During the reporting interval, weekly literature searches were conducted using EMBASE to retrieve relevant publications, pre-publication articles in press, unpublished manuscripts, and abstracts presented at medical or scientific conferences. A total of 91 publications were reviewed, of which 17 publications presented new or significant findings in safety or safety and immunogenicity (n=8, summarized below) or presented significant findings regarding efficacy/effectiveness and/or immunogenicity (n=9, summarized in Section 17.2.2). Citations are presented in Appendix 25.

Review of the 8 publications did not identify any new safety findings that impact the overall benefit-risk balance of Nuvaxovid or Nuvaxovid XBB.1.5.

"Real world Nuvaxovid COVID-19 vaccine safety profile after 100,000 doses in Australia" presented results from the authors' retrospective observational analysis of adverse events following immunisation (AEFI) spontaneously reported to SAFEVAC, the integrated vaccine safety surveillance system used by Victoria and Western Australia, Australia. Reports received from 14-Feb-2022 to 30-Jun-2023 (16.5 months) were analysed for vaccinee demographics, reported reactions and COVID-19 vaccine doses received as reporting rates (RR) per 100,000 doses administered. After 102,946 Doses of Nuvaxovid were administered, 356 AEFI reports were received. Reporting rates were higher after Dose 1 than after Dose 2 (RR 1.5, p=0.0008), after a \ primary series than a booster group (RR 2.4, p< 0.0001), in females than males (RR 1.4, p<0.01), especially in the age range 30-49 years (RR=1.6, p=0.002). Serious AEFI included events of chest pain (n=76, RR=73.8), myocarditis (n=2, RR=1.9) and pericarditis (n=20, RR=19.4). No cases of Guillain-Barré or thrombosis with thrombocytopaenia syndrome were reported, nor deaths attributable to vaccination. This shared SAFEVAC platform enables pooling of clinically reviewed data across jurisdictions, increasing the evidence for the safety profile of Nuvaxovid and improving the odds for identification and description of rare events across all vaccines. [Clothier 2024]

"One-year follow-up of the immunogenicity and safety of a primary series of the NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: Final report of a phase I/II randomized controlled trial" reported results from Part 2 of a randomized, observer-blind, placebo-controlled two-part phase 1/2 clinical trial conducted in Japan on the effects on the immunogenicity and safety of a two-dose primary series of NVX-CoV2373 (TAK-019) or placebo administered 21 days apart to 200 healthy (randomized 3:1) working Japanese adults (≥ 20 years). Part 2 was the open-label, 1-year follow-up of participants who completed Part 1 of the study.131 of the 150 participants in the NVX-CoV2373 arm and 4 of the 50 participants in the placebo arm completed the study. The most common reason for discontinuation was the participant requested a publicly available COVID-19 vaccine. Both immunogenicity (serum IgG titre, neutralizing antibody titre, microneutralization, seroconversion rates) and safety (proportion of participants with serious AEs, medically attended AEs, AESIs, AEs leading to trial withdrawal or discontinuation, and COVID-19 confirmed by a polymerase chain reaction (PCR) test were assessed at 6 months and 1 year after the second vaccine dose. Both the

GMTs of anti-SARS-CoV-2 rS serum IgG and serum nABs against the SARS-CoV-2 ancestral strain were higher than before the second Dose. During the follow-up, there were no deaths, no AEs leading to participant withdrawal, and no AESIs. [Kuriyama 2024]

"Characteristics and Outcomes for Recipients of NVX-CoV2373: A Real-World Retrospective Study in Germany" presented results from a retrospective observational database study to describe the characteristics of NVX-CoV2373 recipients and to explore the impact of NVX-CoV2373 both on tolerability and protection from COVID-19, using the IQVIA German Disease Analyzer database which contains anonymized electronic medical records (including demographics, diagnoses, and prescriptions) from office-based physicians throughout Germany. Data were extracted for 597 individuals who received NVX-CoV2373 as a primary series (58%) or booster (42%) in Germany between 01-Mar-2022 and 31-Dec- 2022, during which Omicron subvariants were the dominant strains. A similar proportion of tolerability-related doctors' visits were reported within 7 days (n = 5; <1%) and 14 days (n = 6; 1%) of vaccination. After a maximum follow up of 10 months (median, 7 months), protection from COVID-19 in the total population was estimated at 95% (95% CI, 93–97). Outcomes were similar across the primary series, booster, and populations with pre-existing comorbidities. The authors concluded that results from this study support the use of NVX-CoV2373 as a primary/booster vaccination for all authorized populations, including those with comorbidities. [Kutikova 2024]

"Unpacking adverse events and associations post COVID-19 vaccination: a deep dive into vaccine adverse event reporting system data" reported results from the authors' analysis of Vaccine Adverse Event Reporting System (VAERS) data from 2020– 2022 to identify potential risk factors for AEs. Using statistical methods (zero-truncated Poisson regression and logistic regression), the authors assessed associations of AEs with age, sex and vaccine manufacturers. Twenty-six System Organ Classes (SOCs) were significantly associated with age and sex. With the exception of 3 SOCs - Neoplasms benign, malignant and unspecified (includes cysts and polyps), Metabolism and nutrition disorders, and Hepatobiliary disorders - 23 SOCs showed statistically significant associations with COVID-19 vaccine manufacturers. Females displayed higher odds in the Pregnancy, puerperium and perinatal conditions SOC, while males had higher odds in the Surgical and medical procedures SOC. Older adults (>65) were more prone to symptoms such as Cardiac disorders, whereas adults 18–65 years showed susceptibility to AEs like Skin and subcutaneous tissue disorders. Moderna and Pfizer vaccines were associated with fewer SOCs compared to Janssen and Novavax vaccines. The zero-truncated Poisson regression model estimated an average 4.243 symptoms per vaccinee averaged across all 4 manufacturers, with the fewest symptoms for the Novavax vaccine (~3.87 per vaccinee) and largest number of symptoms for the Janssen vaccine (~4.8 per vaccinee). [Li 2024]

"Immunogenicity and safety of SARS-CoV-2 recombinant protein subunit vaccine (IndoVac) adjuvanted with alum and CpG 1018 in Indonesian adults: A phase 3, randomized, active-controlled, multicenter trial" reported immunogenicity and safety results through 12 months of a phase 3 randomized, active-controlled, multi-center, prospective interventional study

conducted in 4,050 adults in India of a primary series of IndoVac (PT Bio Farma) with Covovax (Novavax) as the active comparator. In the Covovax group, the incidence rate of AEs through 28 days after the second Dose was 32.15%. Lower numbers of local events were reported compared to systemic events (15.34% and 25.39%, respectively). The most reported solicited AEs were pain (14.43%) followed by myalgia (7.67%) and fatigue (8.68%). Unsolicited AEs varied, with incidence rates under 5%. There were 2 fatal SAEs in the Covovax group, assessed as coincidence (n=1) and unclassifiable (n=1). Most of the AEs in both groups were mild in intensity (27.70%). There were no reports of AESIs nor severe COVID-19 cases throughout the trial. [Nurdin 2024]

"Interstitial lung disease following COVID-19 vaccination: A disproportionality analysis using the Global Scale Pharmacovigilance Database (VigiBase)" presented the results of the authors' investigation of the signals of COVID-19 vaccine-associated interstitial lung disease compared with other vaccinations using disproportionality analysis in the WHO VigiBase database A case/non-case approach was used to assess the disproportionality signal of interstitial lung disease for COVID-19 vaccines via 1:10 matching by age and sex. The first case report of interstitial lung disease after COVID-19 vaccination was published on 09-Jun-2021 and since then several other interstitial lung disease cases were reported. During the 25-month period (12-Dec-2020 to 26-Jan-2023), VigiBase included 1,233,969 ICSRs that reported AEs after a vaccination, of which there were 679 interstitial lung disease cases after a COVID-19 vaccination. The non-case ICSRs were matched by age and sex (10:1) with interstitial lung disease (ILD) ICSRs (6,790 non-ILD cases versus 679 ILD ICSRs). Most of the ILD cases were reported after vaccination with 3 COVID-19 vaccines: tozinameran also known as BNT162b2/Comirnaty (376 reports, 55.4%); Vaxzevria also known as Covishield (129 reports, 19.0%); and elasomeran/Spikevax (78 reports, 11.5%). The non-case study population from VigiBase included 3 cases of AEs other than ILD after NVX-CoV2373 vaccination and no cases of ILD after NVX-CoV2373 vaccination. The authors reported that no significant signal of disproportionate reporting of ILD was observed for COVID-19 vaccines as a group compared with other vaccines (reporting OR 0.86, 95% CI 0.64 to 1.15). [Lee 2023]

"Analysis of Allergy and Hypersensitivity Reactions to COVID-19 Vaccines" reported the results of the authors' original research to identify, analyse, and evaluate the frequency of hypersensitivity reactions to anti-COVID-19 vaccines, regardless of the reported symptoms and allergy mechanism, in the European Economic Area based on the data contained in the EudraVigilance database and vaccination tracker. The total number of administered vaccine Doses extracted on 05-Oct-2023 from Vaccine Tracker included all COVID-19 vaccine administrations to date since vaccinations began in the European Economic Area. As of 05-Oct-2023, 225,312 Doses of NVX-CoV2373 had been administered. The frequency of serious allergic reactions per 100,000 administered vaccine Doses was 1.53 for Comirnaty, 2.16 for Spikevax, 88.6 for Vaxzevria, 2.11 for Janssen, 7.9 for Novavax, 13.3 for VidPrevtyn Beta, and 3.1 for Valneva. The most frequently reported reactions were edema (0.46) and anaphylaxis (0.40). Only 6% of these reactions were delayed hypersensitivity-oriented. The lowest frequency of allergic reaction was observed for Comirnaty and the highest for

Vaxzevria. The overall frequency of potential serious allergic reactions to COVID-19 is very rare. The authors concluded that COVID-19 vaccines are safe for human use. [Romantowski 2024]

"Comparing reactogenicity of COVID-19 vaccine boosters: a systematic review and meta-analysis" presented results from the authors' analysis of publications from 1-Jan-2020 to 1-Jan-2023 describing the reactogenicity of 19 COVID-19 vaccine boosters. Inclusion criteria were blinded, randomized clinical trials of a COVID-19 vaccine booster, the vaccine had reached at least phase III of clinical development, the trial included participants who had previously received an approved COVID-19 primary vaccine, had an intervention and at least one comparator arm (either placebo or a different vaccine) and had assessed safety or reactogenicity. The 19 vaccines included in this systematic review were 3 viral vectors, 5 inactivated, 2 mRNA vaccines and 9 protein subunit vaccines, including 2 NVX-CoV2373 randomised clinical trials. The authors results showed that mRNA vaccines were the most reactogenic, followed by viral vector vaccines and protein sub-unit vaccines, while inactivated vaccines were the least reactogenic. Full-dose vaccines were more reactogenic than half-dose vaccines. Heterologous BNT162b2 boosters were more reactogenic than boosters with the same vaccine used for primary immunisation. [San Francisco Ramos 2024]

12 OTHER PERIODIC REPORTS

Periodic reports submitted to relevant health authorities during the reporting interval by SIIPL (Covovax) and NVX (Nuvaxovid and Nuvaxovid XBB.1.5) are listed in Table 14 below.

No new significant safety related issues were identified from these reports which could change the conclusion of this PBRER.

Table 14: Periodic Summary Safety Reports Submitted to Health Authorities

Periodic Report	Reporting Interval	Submission Countries
Nuvaxovid SSR No.24	01-Dec-2023 to 31-Dec-2023	US
Nuvaxovid SSR No.25	01-Jan-2024 to 31-Jan-2024	US
Covovax PSUR No.03	16-Aug-2023 to 15-Feb-2024	South Africa
Nuvaxovid SSR No.26	01-Feb-2024 to 29-Feb-2024	US
Nuvaxovid SSR No.27	01-Mar-2024 to 31-Mar-2024	US
Nuvaxovid SSR No.28	01-Apr-2024 to 30-Apr-2024	US
Nuvaxovid SSR No.29	01-May-2024 to 31-May-2024	US

SSR: Summary Safety Report, PSUR: Periodic Safety Update Report, US: United States of America

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting interval and cumulatively, no data suggesting lack of efficacy that would constitute a significant risk to the study population was obtained from controlled clinical trials.

14 LATE-BREAKING INFORMATION

No late breaking information with reference to Nuvaxovid's safety, efficacy and effectiveness has been received after the DLP of this PBRER.

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1 Validated Signals During the Reporting Interval

During the reporting interval, two new signals of migraine and tachycardia were validated following health authority requests from Therapeutic Goods Administration (TGA) and US Food and Drug Administration (FDA) respectively. Both the signals were refuted upon evaluation.

The final disposition of a previously validated signal of tinnitus was updated to refuted during the reporting interval in response to US FDA and European Medicines Agency (EMA) reviews and assessments. Tinnitus has been removed from the adverse reactions from post-marketing experience section (Section 4.8) of the CCDS v10.0, effective 30-May-2024 and will remain in the post authorisation section of the Australian Product Information (Section 4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance. See Section 16.2.

A cumulative tabulation of all new, ongoing or closed signals are presented in Appendix 7, Table 33.

15.2 Adverse Events of Special Interest (AESIs)

The following AESIs are being closely monitored based on health authority surveillance recommendations for COVID-19.

- Acute Disseminated Encephalomyelitis
- Anaphylaxis
- Autoimmune Hepatitis
- Autoimmune Thyroiditis
- Bell's Palsy
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Fibromyalgia
- Foetal Growth Restriction
- Myasthenia Gravis
- Myocardial Infarction
- Myocarditis
- Myocarditis and Pericarditis
- Pericarditis
- Narcolepsy
- Neonatal Death
- Oculomotor cranial nerve disorders
- Optic Neuritis
- Postural Orthostatic Tachycardia Syndrome
- Preeclampsia

- Generalised Convulsions
- Gestational Diabetes
- Guillain-Barré Syndrome
- Haemorrhagic Stroke
- Ischaemic Stroke
- Kawasaki's Disease
- Major Congenital Anomalies
- Maternal Death
- Microcephaly
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Preterm Birth
- Rheumatoid Arthritis
- Spontaneous Abortion
- Stillbirth
- Sudden Death
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Transverse Myelitis
- Vaccine-Associated Enhanced Disease
- Venous Thromboembolism

Observed-to-Expected Analysis:

Observed to Expected (O/E) analyses are performed for all Novavax COVID-19 vaccines combined and individually for different variant formulations (Nuvaxovid and Nuvaxovid XBB.1.5). Numerator data are derived from AESI search strategies (Appendix 13). Denominator data are derived from actual and estimated exposure for all formulations combined and separately for each formulation. O/E calculations are not performed for Vaccine Associated Enhanced Disease or pregnancy-related AESIs due to data limitations impacting numerators and/or denominators.

Crude O/E calculations are made prior to the adjudication of cases against standard case definitions for the purpose of signal generation (refer to Appendix 12 for a complete view of O/E tables), with the exception of anaphylaxis for which O/E is performed on both unadjudicated and adjudicated cases pursuant to a request from the EMA. For the remaining unadjudicated O/E calculations, analyses are performed for all AESI for which numerator data have been reported. ICSRs reported from countries/regions with incomplete reporting of ICSRs and/or incomplete reporting of exposure data are excluded from the O/E analysis and therefore summary counts used for O/E may be lower than summary counts used in other parts of the document.

Time-to-onset (TTO) of an AESI is calculated at the individual case level, and may differ from TTO presented in other parts of this document. Risk windows are applied according to published recommendations, and in instances where time to onset (TTO) is unknown, cases are conservatively assessed to fall within a given risk window.

For all AESI, sensitivity analyses are performed to account for underreporting, assuming 50% and 25% of total cases have been reported (refer to Appendix 11 for the sensitivity assumption

and calculation). Based on previous health authority requests, sensitivity analyses on specific risk windows are also conducted for some AESIs.

Further discussions of the limitations of the O/E analyses and the sources of risk window, background incidence rates, administration data, and calculations used for the analyses are presented in Appendix 11.

Overview of AESI Results

The global vaccine safety database was queried for interval and cumulative ICSRs for all AESI using the pre-specified search strategies in Appendix 13. Cumulative O/E analyses were performed up to the DLP of 19-Jun-2024.

Cumulatively up to the DLP of 19-June-2024, no ICSRs were retrieved for the following 10 AESIs for any Nuvaxovid formulation: Acute Disseminated Encephalomyelitis, Foetal Growth Restriction, Gestational Diabetes, Kawasaki's Disease, Major Congenital Anomalies, Maternal Death, Microcephaly, Narcolepsy, Neonatal Death, and Stillbirth.

During the reporting interval, no new AESI signals were validated. When comparing all formulation O/E results to the Nuvaxovid XBB.1.5 formula results, the following O/E results became non-significant:

- On sensitivity analysis for the AESI of generalized convulsions with the assumption of 75% underreporting at the 0 – 1 day risk window, the all-formulation observed rate was significantly greater than expected (RR = 2.13, 95% CI: 1.02 – 3.92). When assessing by vaccine formulation at the 0 – 1 day risk window with the assumption of 75% underreporting, results for Nuvaxovid (RR = 2.20, 95% CI: 0.95 – 4.34) and Nuvaxovid XBB.1.5 (RR = 1.89, 95% CI: 0.23 – 6.82) remained greater than expected, but these results were not statistically significant.

- For the AESIs of myocarditis and myocarditis/pericarditis (0 – 7 day risk window), the all-formulation results for myocarditis (RR=10.42, 95% CI: 6.80 – 15.26) and myocarditis/pericarditis (RR=4.25, 95% CI: 3.34 – 5.32) were statistically significant. When assessing by vaccine formulation, the observed rate for Nuvaxovid XBB.1.5 was greater than expected for myocarditis (RR=2.58, 95% CI: 0.31 – 9.30) and similar to expected for myocarditis/pericarditis (RR=1.00, 95% CI: 0.32 – 2.34) 0 – 7 day risk window, respectively, but these results were not statistically significant. Observed rates for Nuvaxovid XBB.1.5 were significantly greater than expected when assuming 75% underreporting (myocarditis RR=10.30, 95% CI: 1.24 – 37.19); myocarditis/pericarditis RR=4.01, 95% CI: 1.30 – 9.36); 0 – 7 day risk window). Of the 5 ICSRs incorporated into the Nuvaxovid XBB.1.5 O/E analyses, no cases met Brighton Collaboration case definitions Levels 1-3 for either myocarditis or pericarditis. O/E analysis for pericarditis with Nuvaxovid XBB.1.5 showed that the observed rates were not significantly greater than expected for any risk window or on

sensitivity analysis (see Section 15.2.24.2.2 for results). No significant changes in O/E were detected for the remaining AESIs.

O/E results are summarized with each AESI, and full O/E tables are included in Appendix 12. Note: All-Novavax O/E results are included under "Novavax COVID-19 Vaccines," O/E results for Nuvaxovid are included under "Novavax COVID-19 Vaccine, Adjuvanted," and O/E results for Nuvaxovid XBB.1.5 are included under "Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 FORMULA)."

15.2.1 Acute Disseminated Encephalomyelitis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for acute disseminated encephalomyelitis (refer to Appendix 13).

15.2.1.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.1.2 Conclusion

No safety signal was identified.

15.2.2 Anaphylaxis

A signal of anaphylaxis was validated on 18-May-2022, following a request for a label update from TGA. The request was to update the Product Information Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Adverse Effects). As of 27-Jun-2022, the signal of anaphylaxis has been designated as confirmed, based on which, the TGA request to update local Australian Product Information Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable Effects) was fulfilled. Additionally, the CCDS was updated pursuant to the Safety Review Team's decision and a request from EMA in the Pharmacovigilance risk assessment committee (PRAC) Assessment Report for Summary Safety Report (SSR) No. 06 dated 31-Aug-2022 to include anaphylaxis in Section 4.4 and Section 4.8 of the CCDS. A safety variation was approved on 06-Sep-2022.

Anaphylaxis will remain a closely monitored AESI for further characterisation in the post-authorisation setting through routine pharmacovigilance practices and within post-authorisation safety studies and across clinical development programs.

15.2.2.1 Results and Discussion

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for anaphylaxis (refer to Appendix 13).

Cases with Nuvaxovid:

Two initial and one follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 74 ICSRs were retrieved (13 males, 61 females, age range 17 – 75 years, when reported). The 74 cumulative ICSRs included 86 AEs coded to PTs: Anaphylactic reaction (n=47), Anaphylactoid reaction (n=24), Anaphylactic shock (n=7), Circulatory collapse (n=6), Shock (n=1), and Type I hypersensitivity (n=1). All the 86 AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 86 medically significant (based on medical judgement or serious by convention, meeting IME [Important medical event] criteria), 16 hospitalisation, 5 life-threatening and 1 disability.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.2.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Unadjudicated O/E and sensitivity analyses were generated for anaphylaxis using the following risk windows; 0 – 1 day, 0 – 2 days and 0 – 7 days (refer to Table 40).

Refer to Table 15 for a summary of AEs included in the O/E analysis. Results of O/E with sensitivity analysis are presented in Table 16. In addition, cumulative O/E analysis stratified by age and sex is presented in Table 17. O/E was also performed for adjudicated cases and results are presented in Table 18.

Table 15: Summary of AEs Included in O/E Analysis for Anaphylaxis

Parameters	Novavax COVID-19 Vaccines (Unadjudicated)	Novavax COVID-19 Vaccines (Adjudicated)	Nuvaxovid	Nuvaxovid XBB.1.5
Total ICSRs	74	15	74	0
Total AEs included in O/E analysis	74	15	74	0
Number of AEs with TTO reported	67	15	67	–
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	7	0	7	–

Table 15: Summary of AEs Included in O/E Analysis for Anaphylaxis

Parameters	Novavax COVID-19 Vaccines (Unadjudicated)	Novavax COVID-19 Vaccines (Adjudicated)	Nuvaxovid	Nuvaxovid XBB.1.5
AEs with TTO falling outside risk windows				
Risk window 0 – 1 day	6	0	6	–
Risk window 0 – 2 days	4	0	4	–
Risk window 0 – 7 days	3	0	3	–
Total AEs included in O/E analysis stratified by risk window				
Risk window 0 – 1 day	68	15	68	–
Risk window 0 – 2 days	70	15	70	–
Risk window 0 – 7 days	71	15	71	–
Total AEs included in O/E age and gender stratified analysis				
Risk window 0 – 7 days	71	NA	NA	NA

Risk window 0 – 1 day: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 Day (n=68) for all formulation O/E analysis, the unadjudicated observed rate was significantly greater than expected with a rate ratio (RR) of 10.42 (95% CI: 8.09 – 13.21). When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=68) showed the unadjudicated observed rate was significantly greater than expected with an RR of 14.53 (95% CI: 11.28 – 18.42).

Risk window 0 – 2 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=70) for all formulation O/E analysis, the unadjudicated observed rate was significantly greater than expected with an RR of 5.35 (95% CI: 4.17 – 6.76). When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=70) showed the unadjudicated observed rate was significantly greater than expected with an RR of 7.46 (95% CI: 5.82 – 9.43).

Risk window 0 – 7 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=71) for all formulation O/E analysis, the unadjudicated observed rate was significantly greater than expected with an RR of 1.55 (95% CI: 1.21 – 1.96). When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=71) showed the unadjudicated observed rate was significantly greater than expected with an RR of 2.16 (95% CI: 1.69 – 2.73).

Table 16: Unadjudicated O/E Analysis of Anaphylaxis with Sensitivity Analysis for All Cumulative AEs

Risk Window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
Novavax COVID-19 Vaccines			
0 – 1 Day	10.42 (8.09 – 13.21) *	20.83 (16.18 – 26.41) *	41.66 (32.35 – 52.82) *
0 – 2 Days	5.35 (4.17 – 6.76) *	10.71 (8.35 – 13.53) *	21.42 (16.70 – 27.06) *
0 – 7 Days	1.55 (1.21 – 1.96) *	3.11 (2.43 – 3.92) *	6.21 (4.85 – 7.83) *
Nuvaxovid			
0 – 1 Day	14.53 (11.28 – 18.42) *	29.05 (22.56 – 36.83) *	58.11 (45.12 – 73.67) *
0 – 2 Days	7.46 (5.82 – 9.43) *	14.93 (11.64 – 18.86) *	29.85 (23.27 – 37.72) *
0 – 7 Days	2.16 (1.69 – 2.73) *	4.33 (3.38 – 5.46) *	8.65 (6.76 – 10.92) *
Nuvaxovid XBB.1.5			
0 – 1 Day	Not applicable	Not applicable	Not applicable
0 – 2 Days	Not applicable	Not applicable	Not applicable
0 – 7 Days	Not applicable	Not applicable	Not applicable

* Increased and statistically significant O/E results.

15.2.2.2.1 Results of Unadjudicated O/E Analysis stratified by Age and Sex

The results of unadjudicated O/E analysis for anaphylaxis with a 7-Day risk window, stratified by age and sex, are presented in Table 17 below. When accounting for all cumulative anaphylaxis reports meeting inclusion criteria (n=71) stratified by age and sex; the unadjudicated observed rate as reported in the total male group (n=12) was significantly greater than expected with an RR of 5.71 (95% CI: 2.95 – 9.97). Statistically significant increases were seen in the 20 – 29-year-old male group (n=2) with an RR of 8.84 (95% CI: 1.06 – 31.91) and the 40 – 49-year-old male group (n=3) with an RR of 7.96 (95% CI: 1.65 – 23.28). The unadjudicated observed rate as reported in the total female group (n=59) was significantly greater than expected with an RR of 11.20 (95% CI: 8.52 – 14.44). Results showed a statistically significant increase in the 0 – 19-year-old female group (n=5) with an RR of 51.78 (95% CI: 16.78 – 120.86), in the 20 – 29-year-old female group (n=4) with an RR of 7.36 (95% CI: 2.01 – 18.85), in the 30 – 39-year-old female group (n=15) with an RR of 13.63 (95% CI: 7.63 – 22.47), in the 40 – 49-year-old female group (n=20) with an RR of 16.16 (95% CI: 9.87 – 24.96), the 50 – 59-year-old female group (n=11) with an RR of 9.53 (95% CI: 4.76 – 17.05), and in the 60 – 69-year-old female group (n=4) with an RR of 5.44 (95% CI: 1.48 – 13.92).

Table 17: Unadjudicated O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Doses				
0 – 19	0	0 (0 – 22.01)	5	51.78 (16.78 – 120.86) *
20 – 29	2	8.84 (1.06 – 31.91) *	4	7.36 (2.01 – 18.85) *
30 – 39	2	6.33 (0.76 – 22.86)	15	13.63 (7.63 – 22.47) *
40 – 49	3	7.96 (1.65 – 23.28) *	20	16.16 (9.87 – 24.96) *
50 – 59	1	2.54 (0.08 – 14.13)	11	9.53 (4.76 – 17.05) *
60 – 69	1	2.61 (0.08 – 14.56)	4	5.44 (1.48 – 13.92) *
70 – 79	0	0 (0 – 18.89)	0	0 (0 – 11.74)
80+	0	0 (0 – 85.32)	0	0 (0 – 42.21)
Missing	3	N/A	0	N/A
Total	12	5.71 (2.95 – 9.97) *	59	11.20 (8.52 – 14.44) *

* Increased and statistically significant O/E results.

15.2.2.3 Results of O/E Anaphylaxis following Adjudication (Overall Dose Series)

Of the 71 ICSRs retrieved by the AESI search strategy for anaphylaxis and subsequently adjudicated against the established Brighton Collaboration case definition for Anaphylaxis, 15 cases were adjudicated to Brighton Collaboration Level 1 – 3 criteria. O/E analyses were generated for anaphylaxis for adjudicated cases using the following risk windows; 0 – 1 day, 0 – 2 days and 0 – 7 days (Refer to Table 40). A TTO of 0 was reported for all 15 adjudicated cases and therefore all cases (n=15) were included in the analyses for all risk windows. An all-Novavax COVID-19 O/E analysis for adjudicated cases was performed in addition to formulation-specific O/E analyses.

Refer to Table 18 for O/E results following adjudication, for Brighton Collaboration Level 1 – 3 anaphylaxis cases.

Table 18: O/E Analysis (Brighton Collaboration Levels 1-3) following Adjudication – All Cumulative adjudicated AEs

Risk Window	O/E Rate Ratio (95 % CI)
Novavax COVID-19 Vaccines	
0 – 1 Day	2.30 (1.29 – 3.79) *
0 – 2 Days	1.15 (0.64 – 1.89)
0 – 7 Days	0.33 (0.18 – 0.54) **

Table 18: O/E Analysis (Brighton Collaboration Levels 1-3) following Adjudication – All Cumulative adjudicated AEs

Risk Window	O/E Rate Ratio (95 % CI)
Nuvaxovid	
0 – 1 Day	3.20 (1.79-5.29) *
0 – 2 Days	1.60 (0.90-2.64)
0 – 7 Days	0.46 (0.26 – 0.75) **
Nuvaxovid XBB.1.5	
0 – 1 Day	Not applicable
0 – 2 Days	Not applicable
0 – 7 Days	Not applicable

* Increased and statistically significant O/E results.

** Decreased and statistically significant O/E results.

Risk window 0 – 1 day: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 Day (n=15) for all formulation O/E analysis, the observed rate was significantly greater than expected with an RR of 2.30 (95% CI: 1.29 – 3.79). When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=15) showed the adjudicated observed rate was significantly greater than expected with an RR of 3.20 (95% CI: 1.79 – 5.29).

Risk window 0 – 2 days: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=15) for all formulation O/E analysis, the observed rate was greater than expected, but not statistically significant. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=15) showed the adjudicated observed rate was greater than expected, but not statistically significant.

Risk window 0 – 7 days: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=15) for all formulation O/E analysis, results were not increased. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=15) showed the results were not increased.

15.2.2.4 Limitations of O/E Analysis Stratified by Age and Sex

Demographic information on age was only available in exposure data from Australia, EU, Switzerland, Japan, New Zealand and UK, and none of the countries or regions reported the exposure data in the age categories requested. In addition, only the UK provides exposure data by sex. As proposed by Mahaux 2016, the demographic distributions of the observed reports can be used to approximate the missing demographic distributions in exposure data. Therefore, the proportion of the observed count of reports (including all AEs) received from a

given strata compared to the total count of reports received was applied to the exposure data to obtain the stratum-specific exposure data. However, this methodology may lead to substantially biased distributions of the exposure across strata due to differential reporting rates across ages and sexes. Differential spontaneous reporting rates by age and sex have been well documented following vaccinations, including COVID-19 vaccinations [Xiong 2021]. In summary, the currently available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable.

15.2.2.5 Limitations to O/E Analysis Following Adjudication

The limitations to O/E of adjudicated cases are similar to the general limitations of O/E analysis discussed in Appendix 11.

15.2.2.6 Conclusion

A total of 74 ICSRs were reported cumulatively. There were 71 AEs that met inclusion criteria for the unadjudicated observed count for all formulation O/E analyses for the 0 – 7 days risk window. The unadjudicated O/E results revealed a significantly greater observed rate compared to the expected for all formulation O/E analysis and when assessing by vaccine formulation for Nuvaxovid. No AEs have been reported for Nuvaxovid XBB.1.5. O/E results also showed a greater than expected observed rate for the 0 – 1 and 0 – 2 Day risk windows for all formulation O/E analysis and when assessing by vaccine formulation for Nuvaxovid. Results for all reports stratified by age and sex were statistically significant for the total male group, males 20 – 29 years, males 40 – 49 years, females 0 – 69 years, and the total female group.

A total of 15 case reports met Brighton Collaboration case Levels 1 – 3 for anaphylaxis and were included in the adjudicated analysis. Overall, results showed that when only adjudicated cases are considered, for all formulation O/E analyses and when assessing by vaccine formulation for Nuvaxovid, the O/E remains increased and statistically significant for a 0 – 1 Day risk window.

This AESI underwent complete signal evaluation and was confirmed as a signal. Anaphylaxis was added to the RSI section of the Investigators Brochure and the CCDS was updated to include anaphylaxis following administration of Nuvaxovid in Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable Effects). The AESI of anaphylaxis will continue to be monitored for further characterisation of the risk, via routine pharmacovigilance activities.

15.2.3 Autoimmune Hepatitis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for autoimmune hepatitis (refer to Appendix 13)

15.2.3.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, age range 44 – 57 years). The 2 cumulative ICSRs included 2 AEs coded to PT: Autoimmune hepatitis (n=2). Of the 2 AEs reported, 2 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.3.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO for 1 of the 2 AEs was reported as 92 days, which fell outside the risk window of 0 – 42 days (refer to Table 40). The TTO was not reported for the other AE and was conservatively included in the O/E analyses. Therefore, 1 AE met the inclusion criteria for the observed count (n=1). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid remained similar to all formulation O/E analysis.

15.2.3.3 Conclusion

One ICSR met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.4 Autoimmune Thyroiditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for autoimmune thyroiditis (refer to Appendix 13).

15.2.4.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (3 females, ages 34 – 42 years). The 3 cumulative ICSRs included 3 AEs coded to PTs: Autoimmune Thyroiditis (n=1), Graves' disease (n=1) and Thyroiditis (n=1). Of the 3 AEs reported, 2 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 disability.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.4.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO was not reported for any of the 3 AEs, and they were conservatively assumed to fall within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid remained similar to all formulation O/E analysis.

15.2.4.3 Conclusion

Three ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.5 Bell's Palsy

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for Bell's Palsy (refer to Appendix 13).

15.2.5.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 24 ICSRs were retrieved (10 males, 14 females, age range 20 – 77 years). The 24 cumulative ICSRs included 26 AEs coded to PTs: Facial paralysis (n=21), Bell's palsy (n=3), Facial nerve disorder (n=1), and Facial paresis (n=1). Of the 26 AEs reported, 25 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 24 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 5 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

One initial and 1 follow-up ICSRs have been retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, age range 34 – 42 years). The 2 cumulative ICSRs included 3 AEs coded to PTs: Bell's palsy (n=1), Facial paralysis (n=1), and Facial paresis (n=1). Of the 3 AEs reported, 3 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

15.2.5.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO for 22 of 25 ICSRs ranged from 0 – 25 days, which were within the risk window of 0 – 42 days (refer to Table 40). TTO was not reported for the other 3 AEs and these AEs were conservatively included in the O/E analyses. Therefore 25 AEs met inclusion criteria for the observed count (n=25). O/E and sensitivity analyses showed that all formulation unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=24) and Nuvaxovid XBB.1.5 (n=1) showed that the unadjudicated observed rate was lower than the expected rate.

15.2.5.3 Conclusion

Twenty-five AEs met TTO inclusion criteria and results of the O/E and sensitivity analyses showed lower than expected rates.

No safety signal was identified.

15.2.6 Cerebral Venous Sinus Thrombosis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for cerebral venous sinus thrombosis (refer to Appendix 13).

15.2.6.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, 67 years). This 1 cumulative ICSR included 1 serious AE coded to PT: Cerebral venous sinus thrombosis, meeting the following criterion: medically significant (meeting IME criteria).

Of note, because the PT cerebral venous sinus thrombosis is included in the search strategy for the AESI Venous Thromboembolism, the same ICSR was also retrieved in the search results for Venous Thromboembolism (Section 15.2.40).

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.6.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For the all formulation O/E analysis, the TTO for this single AE was reported as 1 day, which fell within the risk window of 0 – 28 days (refer to Table 40) and met inclusion criteria for the observed count (n=1). O/E and 50% underreporting sensitivity analysis showed that the observed rate was decreased and not statistically significant but when assuming 75% underreporting, results showed a non-statistically significant increase. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid remained similar to all formulation O/E analysis.

15.2.6.3 Conclusion

The single ICSR met TTO inclusion criteria and O/E analysis showed the observed count was increased compared to the expected count at 75% sensitivity analysis, but this increase was not statistically significant.

No safety signal was identified.

15.2.7 Chronic Fatigue Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for chronic fatigue syndrome (refer to Appendix 13).

15.2.7.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (2 males and 1 female, ages 32 – 45 years). The 3 cumulative ICSRs included 3 AEs coded to PT: Chronic fatigue syndrome. Of the 3 AEs reported, 1 was serious, with the event meeting the following criteria: 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.7.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO for 1 of 3 AEs was reported as 1 day, which was within the risk window of 0 – 42 days (refer to Table 40). The TTO was not reported for 1 AE and this AE was conservatively included in the O/E analyses. The TTO for the remaining AE was reported as 328 days, which fell outside of the risk window. Therefore, after excluding the AE that fell outside the risk window, 2 AEs met inclusion criteria for the observed count (n=2). Unadjudicated O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid remained similar to all formulation O/E analysis.

15.2.7.3 Conclusion

Two AEs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for all formulation and Nuvaxovid vaccine analyses.

No safety signal was identified.

15.2.8 Encephalitis and Encephalomyelitis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for encephalitis and encephalomyelitis (refer to Appendix 13).

15.2.8.1 Results and Discussion

Cases with Nuvaxovid:

One initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (3 males, 2 females, age range 42 – 67 years). The 5 ICSRs included 5 AEs coded to PTs of Noninfective encephalitis (n=2) and Encephalitis (n=3). All 5 reported AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 5 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.8.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for 2 of 5 AEs were reported as 1 day and 28 days, both of which fell within the risk window of 0 – 42 days (refer to Table 40). The TTO was not reported for the other 3 AEs, and they were conservatively included in the O/E analyses. Therefore, all AEs met the inclusion criteria for the observed count (n=5). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=5) remained similar to all formulation O/E analysis.

15.2.8.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.9 Fibromyalgia

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for fibromyalgia (refer to Appendix 13).

15.2.9.1 Results and Discussion

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (1 male, 3 females, age range 49 – 50 years, when reported). The 4 cumulative ICSRs included 4 non-serious AEs coded to the PT Fibromyalgia (n=4).

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, age 60 years). This ICSR included 1 non-serious AE coded to PT: Fibromyalgia (n=1).

15.2.9.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for 2 of 5 AEs were reported as 1 day and 2 days, both of which fell within the risk window of 0 – 42 days (refer to Table 40). The TTO was not reported for the other 3 AEs, and they were conservatively included in the O/E analyses. Therefore, all AEs met the inclusion criteria for the observed count (n=5). O/E and sensitivity analyses results showed the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=4) and Nuvaxovid XBB.1.5 (n=1) showed that the unadjudicated observed rate was lower than the expected rate.

15.2.9.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.10 Foetal Growth Restriction

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for foetal growth restriction (refer to Appendix 13).

15.2.10.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.11 Generalised Convulsions

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for generalised convulsions (refer to Appendix 13).

15.2.11.1 Results and Discussion

Cases with Nuvaxovid:

No initial or follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 13 ICSRs were retrieved (3 males, 10 females, age range 17 – 76 years). The 13 cumulative ICSRs included 14 AEs coded to PTs: Seizure (n=8), Epilepsy (n=2), Clonic convulsion (n=1), Febrile convulsion (n=1), Generalised tonic-clonic seizure (n=1), and Postictal state (n=1). Of the 14 AEs reported, 13 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 13 medically

significant (based on medical judgement or serious by convention, meeting IME criteria), 4 hospitalisation, 2 life-threatening, and 1 death.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (1 female, 1 male, 42 and 72 years, respectively) and included 2 serious AEs coded to PT: Seizure (n=2), with the events meeting the medically significant (based on medical judgement or serious by convention, meeting IME criteria) seriousness criterion.

15.2.11.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Multiple sets of O/E and sensitivity analyses were completed for generalised convulsions using the following risk windows: 0 – 1 day, 0 – 2 days, and 0 – 7 days (refer to Table 40). Two reports, 1 with 2 AEs having a TTO of 92 days and the other with a TTO of 38 days, fell outside the risk windows and were excluded from O/E analyses. The TTO was not reported for 2 AEs, and both were conservatively included in the O/E analyses. The TTO was known for the other 11 AEs, which fell within the 0 –7 Day risk window and ranged from 0 – 6 days. Thirteen AEs met the inclusion criteria for the observed count (n=13) for O/E analyses for a risk window of 0 – 7 days.

Risk window 0 – 1 day: When accounting for all cumulative generalised convulsions AEs meeting inclusion criteria within a risk window of 0 – 1 Day (n=10) for all formulation O/E analysis, the unadjudicated observed rate was lower than the expected rate. When assuming 75% underreporting, the unadjudicated observed rate was significantly greater than expected with an RR of 2.13 (95% CI: 1.02 – 3.92). When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=8) and Nuvaxovid XBB.1.5 (n=2) results remained greater than expected at 75% underreporting, but these results were not statistically significant.

Additional risk windows: For all formulation O/E analysis, when accounting for all cumulative generalised convulsions AEs meeting inclusion criteria, multiple O/E analyses were completed using risk windows of 0 – 7 days (n=13) and 0 – 2 days (n=11) and each showed that the overall unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid XBB.1.5 and for Nuvaxovid remained similar to all formulation O/E analysis.

O/E results based on multiple risk windows for generalised convulsions are included in Appendix 12.

15.2.11.3 Conclusion

Thirteen AEs met inclusion criteria for all formulation O/E analyses for the 0 – 7-Day risk window. O/E analysis showed that the unadjudicated observed rate was lower than the expected rate for risk windows 0 – 1, 0 – 2 and 0 – 7 days. O/E analysis calculated using a risk window of 0 – 1 days showed the unadjudicated observed count was significantly greater than expected at 75% sensitivity for all formulation O/E analysis, but not when stratified by vaccine formulation.

No safety signal was identified.

15.2.12 Gestational diabetes

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for gestational diabetes (refer to Appendix 13).

15.2.12.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.13 Guillain-Barré Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for Guillain-Barré syndrome (refer to Appendix 13).

15.2.13.1 Results and Discussion

Cases with Nuvaxovid:

Two initial ICSRs have been retrieved for the current reporting interval.

Cumulatively, 10 ICSRs were retrieved (6 males, 3 females, 1 of unknown sex, age range 18 – 82 years, when reported). The 10 cumulative ICSRs included 10 serious AEs coded to PT: Guillain-Barré syndrome with the events meeting the following criteria (an event may meet more than one seriousness criterion): 10 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 2 hospitalisation, 1 life threatening and 2 disability.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.13.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO for 5 of 10 AEs ranged from 0 to 12 days, which fell within the risk window of 0 – 42 days (refer to Table 40). TTO for 2 AEs fell outside the risk window and were excluded. The TTO for the remaining 3 AEs were not reported and were conservatively included in the O/E analysis. Therefore, 8 AEs met inclusion criteria for the observed count (n=8). The observed rate was lower than the expected rate. At 50% underreporting the unadjudicated observed rate was greater than expected, but this increase was not statistically significant. However, when assuming 75% underreporting, there was a statistically significant increase in the observed rate versus the expected rate with an RR of 3.22 (95% CI: 1.39 – 6.34). When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5. For Nuvaxovid (n=8) the observed rate was greater than expected, but this increase was not statistically significant unless assuming 75% underreporting with an RR of 4.65 (95% CI: 2.01 – 9.17).

15.2.13.3 Conclusion

Eight ICSRs met TTO inclusion criteria for O/E analyses. The unadjudicated observed rate was increased compared to the expected rate at 50% underreporting, but this increase was not statistically significant unless assuming 75% underreporting for all formulation O/E analysis and the O/E analysis for the Nuvaxovid formulation.

No safety signal was identified.

15.2.14 Haemorrhagic Stroke

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for haemorrhagic stroke (refer to Appendix 13).

15.2.14.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 11 ICSRs were retrieved (7 males, 4 females, age range 20 – 96 years, when reported). The 11 cumulative ICSRs included 11 AEs coded to the PT of Cerebrovascular accident. All the 11 reported AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 11 medically significant (based on

medical judgement or serious by convention, meeting IME criteria), 7 hospitalisation, 1 life-threatening, 1 disability, and 2 death.

Of note, the same 11 ICSRs were also retrieved by the search strategy for Ischaemic stroke (Section 15.2.15).

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.14.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, the TTO for 4 out of 11 AEs ranged from 1 to 10 days which fell within the risk window of 0 – 28 days (refer to Table 40). TTO was not reported for 3 AEs and conservatively included in the O/E analysis. The TTO for the remaining 4 AEs ranged from 31 days to 67 days, hence fell outside the risk window. Therefore, excluding 4 AEs falling outside the risk window, a total of 7 AEs met inclusion criteria for the observed count (n=7). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=7) remained similar to all formulation O/E analysis.

15.2.14.3 Conclusion

Seven ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed a lower-than-expected rate.

No safety signal was identified.

15.2.15 Ischaemic Stroke

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for ischaemic stroke (refer to Appendix 13).

15.2.15.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 17 ICSRs were retrieved (9 males, 8 females, age range 20 – 96 years, when reported). The 17 cumulative ICSRs included 17 AEs coded to PTs: Cerebrovascular accident (n=11), Transient Ischaemic Attack (n=2), Brain stem infarction (n=1), Carotid artery disease (n=1), Cerebral infarction (n=1) and Ischaemic stroke (n=1). All 17 reported AEs were

serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 17 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 11 hospitalisation, 2 life-threatening, 2 disability, and 2 death.

Of note, 11 of the 17 ICSRs were also retrieved by the search strategy for Haemorrhagic stroke (Section 15.2.14).

Cases with Nuvaxovid XBB.1.5:

Two initial ICSRs have been retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (females, ages 82 and 42 years). These 2 cumulative ICSRs included 2 AEs coded to PTs: Ischaemic stroke (n=1) and Transient Ischaemic Attack (n=1). Both reported AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

15.2.15.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

The TTO for 11 of 19 AEs ranged from 1 – 21 days which fell within the risk window of 0 – 28 days (refer to Table 40). TTO was not reported in 4 of the 19 AEs and these AEs were conservatively included in O/E analysis. TTO for the remaining 4 AEs ranged from 31 days to 67 days, hence fell outside the risk window. Therefore, after excluding the 4 AEs falling outside the risk window, 15 AEs met inclusion criteria for the observed count (n=15) for O/E analysis. O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid XBB.1.5. (n=2) and Nuvaxovid (n=13) remained similar to all formulation O/E analysis.

15.2.15.3 Conclusion

Fifteen ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.16 Kawasaki's Disease

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for Kawasaki's Disease (refer to Appendix 13).

15.2.16.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.16.2 Conclusion

No safety signal was identified.

15.2.17 Major Congenital Anomalies

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for major congenital anomalies (refer to Appendix 13).

15.2.17.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.18 Maternal Death

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for maternal death (refer to Appendix 13).

15.2.18.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.19 Microcephaly

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for microcephaly (refer to Appendix 13).

15.2.19.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.20 Multiple Sclerosis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for multiple sclerosis (refer to Appendix 13).

15.2.20.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (1 male, 2 females, age range 36 – 63 years). The 3 cumulative ICSRs included 3 AEs coded to PTs: Multiple sclerosis relapse (n=2), and Multiple sclerosis (n=1). All 3 reported AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 3 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 disability.

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.20.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO of the 3 AEs ranged from 0 – 2 days which were within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation,

no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=3) remained similar to all formulation O/E analysis.

15.2.20.3 Conclusion

All ICSRs met the TTO inclusion criteria and the results of unadjudicated O/E analyses showed a lower than the expected rate.

No safety signal was identified.

15.2.21 Multisystem Inflammatory Syndrome in Children

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for multisystem inflammatory syndrome in children (refer to Appendix 13).

15.2.21.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, no cases were retrieved involving children and 1 ICSR was retrieved for an adult (1 female, age 82 years). The single ICSR included 1 AE coded to PT: Multisystem inflammatory syndrome (n=1) and was serious due to medically significant (based on medical judgement or serious by convention, meeting IME criteria) and hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.21.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO was reported as 8 days for this single report, which fell within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=1) remained similar to all formulation O/E analysis.

15.2.21.3 Conclusion

The single ICSR met TTO inclusion criteria and results of the O/E and sensitivity analyses showed lower than expected rates.

No safety signal was identified.

15.2.22 Myasthenia Gravis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for myasthenia gravis (refer to Appendix 13).

15.2.22.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, age 69 years). This single ICSR included 1 AE coded to PT Myasthenia Gravis, which was serious, meeting the following criteria: medically significant (meeting IME criteria) and hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.22.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO was reported as 23 days for this single report which fell within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=1) remained similar to all formulation O/E analysis.

15.2.22.3 Conclusion

The single ICSR met the TTO inclusion criterion and results of the O/E sensitivity analyses showed lower than expected rates.

No safety signal was identified.

15.2.23 Myocardial Infarction

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for myocardial infarction (refer to Appendix 13).

15.2.23.1 Results and Discussion

Cases with Nuvaxovid:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 16 ICSRs were retrieved (9 males, 7 females, age range 24 – 93 years, when reported). The 16 cumulative ICSRs included 16 AEs coded to PTs: Troponin increased (n=7), Myocardial infarction (n=4), Acute myocardial infarction (n=3), Acute coronary syndrome (n=1), and Coronary artery thrombosis (n=1). Of the 16 AEs reported, 13 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 12 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 9 hospitalisation, 1 life-threatening, and 1 death.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.23.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for 7 of 16 AEs ranged from 0 – 14 days, which fell within the risk window of 0 – 28 days (refer to Table 40). Five AEs with TTOs ranging from 60 to 130 days fell outside the risk window and, hence, were excluded from the O/E analysis. TTOs were not reported for the remaining 4 AEs, which were conservatively included in the O/E analyses. Therefore, 11 of 16 AEs met TTO inclusion criteria for the observed count (n=11) for O/E analysis. O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=11) remained similar to all formulation O/E analysis.

15.2.23.3 Conclusion

Eleven AEs met the TTO inclusion criterion and results of the O/E analyses showed lower than expected rate.

No safety signal was identified.

15.2.24 Myocarditis and Pericarditis

A signal of myocarditis and pericarditis was validated on 17-May-2022 and a signal evaluation was completed. On 03-Aug-2022, the signal of myocarditis and pericarditis was confirmed. The CCDS was updated to include Myocarditis and Pericarditis in Section 4.4

(Special Warnings and Precautions for use) and Section 4.8 (Undesirable effects). Further details and analysis are provided in Section 16.3.1.1.

Myocarditis and Pericarditis remains a closely monitored AESI for further characterisation in the post-authorisation setting through routine pharmacovigilance practices, within post-authorisation safety studies, and across clinical development programs.

15.2.24.1 Myocarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for myocarditis (refer to Appendix 13).

15.2.24.1.1 Results and Discussion

Cases with Nuvaxovid:

One initial and one follow-up ICSR were retrieved for the current reporting interval.

Cumulatively, 31 ICSRs were retrieved (15 males, 16 females, age range 18 – 83 years, when reported). The 31 cumulative ICSRs included 31 AEs coded to PTs: Myocarditis (n=24) and Myopericarditis (n=7). Of the 31 AEs reported, 31 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 31 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 9 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (1 female, 1 individual of unknown sex, ages not reported). The 2 cumulative ICSRs included 2 AEs coded to PTs: Myocarditis (n=1) and Myopericarditis (n=1). Of the two AEs reported, 2 were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

15.2.24.1.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Multiple sets of unadjudicated O/E and sensitivity analyses were completed for myocarditis using the following risk windows: 0 – 7 days, 0 – 14 days, 0 – 30 days, and 0 – 42 days (refer to Table 40). TTOs were reported for 19 of the 33 AEs and were unknown for the remaining 14 AEs which were conservatively assessed as falling within the risk window. The TTO ranged from 0 – 21 days in 17 of the 19 AEs with known TTO. For the other 2 AEs with

known TTO, they were reported as 102 days and 137 days, which fell outside all risk windows.

Refer to Table 19 for the stratification of AEs included in unadjudicated O/E analysis.

Table 19: Stratification of AEs Included in Unadjudicated O/E Analysis for Myocarditis

Parameters	**Novavax COVID-19 Vaccines, Unadjudicated**	**Nuvaxovid**	**Nuvaxovid XBB.1.5**
Total ICSRs	33	31	2
Total AEs	33	31	2
Number of AEs with TTO reported	19	19	0
Number of AEs with TTO missing (conservatively assessed as falling within the risk window)	14	12	2
AEs with TTO falling outside risk windows			
Risk window 0 – 7 days	7	7	0
Risk window 0 – 14 days	5	5	0
Risk window 0 – 30 days	2	2	0
Risk window 0 – 42 days	2	2	0
Total AEs included in O/E analysis stratified by risk window			
Risk window 0 – 7 days	26	24	2
Risk window 0 – 14 days	28	26	2
Risk window 0 – 30 days	31	29	2
Risk window 0 – 42 days	31	29	2
Total AEs included in O/E age and gender stratified analysis			
Risk window 0 – 42 days	31	NA	NA

Risk window 0 – 7 days: When accounting for all formulation cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=26), the unadjudicated observed rate was significantly greater than expected with an RR of 10.42 (95% CI:6.80 – 15.26). When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=24) with an RR of 13.95 (95% CI: 8.94 – 20.76) but increased and not statistically significant for Nuvaxovid XBB.1.5 (n=2).

Risk window 0 – 14 days: When accounting for all formulation cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=28), the unadjudicated observed rate was significantly greater than expected with an RR of 5.61 (95% CI: 3.73 – 8.10). When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=26) with an RR of

7.56 (95% CI: 4.94 – 11.07) but increased and not statistically significant for Nuvaxovid XBB.1.5 (n=2).

Risk window 0 – 30 days: When accounting for all formulation cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=31), the unadjudicated observed rate was significantly greater than expected with an RR of 3.06 (95% CI: 2.08 – 4.34). When assessing by dose formulation for the vaccine, unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=29) with an RR of 4.26 (95% CI: 2.85 – 6.12) but lower than expected for Nuvaxovid XBB.1.5 (n=2).

Risk window 0 – 42 days: When accounting for all formulation cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=31), the unadjudicated observed rate was significantly greater than expected with an RR of 2.27 (95% CI: 1.54 – 3.22). When assessing by dose formulation for the vaccine, unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=29) with an RR of 3.22 (95% CI: 2.16 – 4.63) but lower than expected for Nuvaxovid XBB.1.5 (n=2).

Table 20: Unadjudicated O/E Analysis of Myocarditis with Sensitivity Analysis for All Cumulative AEs

Risk window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
Novavax COVID-19 Vaccines			
0 – 7 Days	10.42 (6.80 – 15.26) *	20.83 (13.61 – 30.53) *	41.67 (27.21 – 61.06) *
0 – 14 Days	5.61 (3.73 – 8.10) *	11.22 (7.45 – 16.21) *	22.43 (14.91 – 32.42) *
0 – 30 Days	3.06 (2.08 – 4.34) *	6.12 (4.16 – 8.68) *	12.24 (8.31 – 17.37) *
0 – 42 Days	2.27 (1.54 – 3.22) *	4.54 (3.08 – 6.44) *	9.08 (6.17 – 12.89) *
Nuvaxovid			
0 – 7 Days	13.95 (8.94 – 20.76) *	27.91 (17.88 – 41.52) *	55.82 (35.77 – 83.05) *
0 – 14 Days	7.56 (4.94 – 11.07) *	15.11 (9.87 – 22.15) *	30.23 (19.74– 44.30) *
0 – 30 Days	4.26 (2.85 – 6.12) *	8.52 (5.71 – 12.24) *	17.04 (11.41 – 24.48) *
0 – 42 Days	3.22 (2.16 – 4.63) *	6.44 (4.32 – 9.26) *	12.89 (8.63 – 18.51) *
Nuvaxovid XBB.1.5			
0 – 7 Days	2.58 (0.31 – 9.30)	5.15 (0.62– 18.59)	10.30 (1.24 – 37.19) *
0 – 14 Days	1.29 (0.15 – 4.65)	2.58 (0.31 – 9.30)	5.15 (0.62 – 18.60)
0 – 30 Days	0.60 (0.07 – 2.17)	1.20 (0.14 – 4.34)	2.40 (0.29 – 8.68)
0 – 42 Days	0.43 (0.05 – 1.55)	0.86 (0.10 – 3.10)	1.72 (0.21 – 6.21)

* Increased and statistically significant O/E results

15.2.24.1.2.1 Results of Unadjudicated O/E Analysis Stratified by Age and Sex

When accounting for all formulation cumulative myocarditis AESI reports (n=31), stratified by age and sex with a risk window of 0 – 42 days, the unadjudicated observed rate as reported

in the total male group (n=14) was significantly greater than expected with an RR of 1.94 (95% CI: 1.06 – 3.26). The unadjudicated observed rate was significantly greater than expected for the total female group (n=16) with an RR of 2.50 (95% CI: 1.43 – 4.05). This was also the case for the 0 – 19-year-old male group (n=3) with an RR of 22.98 (95% CI: 4.75 – 67.17) and in the 20 – 29-year-old female group (n=6) with an RR of 12.58 (95% CI: 4.61 – 27.38).

Table 21: Unadjudicated O/E Analysis of Myocarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	3	22.98 (4.75 – 67.17) ***	0	0 (0 – 104.85)
20 – 29	2	1.53 (0.18 – 5.51)	6	12.58 (4.61 – 27.38) ***
30 – 39	3	1.79 (0.37 – 5.23)	1	0.86 (0.03 – 4.79)
40 – 49	3	2.15 (0.44 – 6.29)	3	2.49 (0.51 – 7.27)
50 – 59	1	1.07 (0.03 – 5.94)	3	2.35 (0.49 – 6.87)
60 – 69	0	0 (0 – 4.07)	0	0 (0 – 3.04)
70 – 79	0	0 (0 – 6.07)	1	1.42 (0.04 – 7.92)
80+	1	4.19 (0.13 – 23.32)	0	0 (0 – 11.06)
Missing	1	N/A	2	N/A
Total	14 *	1.94 (1.06 – 3.26) ***	16 **	2.50 (1.43 – 4.05) ***

* One AE with TTO of 102 days fell outside all risk windows

**One AE with TTO of 137 days fell outside all risk windows

*** Increased and statistically significant O/E results.

15.2.24.1.2.2 Limitations to O/E Analysis Stratified by Age and Sex

Demographic information on age and sex was only available in exposure data from Australia, EU, Switzerland, Japan, UK and New Zealand, and none reported the exposure data in the age categories requested. In addition, only the UK provides data on patient sex. As proposed by Mahaux 2016, the demographic distributions of the observed reports could be used to approximate the missing demographic distributions in exposure data. Therefore, the proportion of the observed count of reports (including all AEs) received from a given stratum compared to the total count of reports received was applied to the exposure data to get the stratum-specific exposure data currently. However, this methodology may lead to substantially biased distributions of the exposure across strata due to differential reporting rates across ages and sexes. This bias is likely to be enhanced due to the small number of cases in the stratum. Additionally, age- and sex-related differences in spontaneous reporting rates following vaccination (including COVID-19 immunisation) are well documented in the

literature [Xiong 2021]. In summary, the current available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable.

15.2.24.1.3 Conclusion

The increase in the all formulation-Novavax observed rate compared to expected rate was statistically significant for all risk windows overall and with Nuvaxovid. An increase was observed for the Nuvaxovid XBB1.5. formulation at 75% underreporting for the 0 – 7 day risk window.

Results of the unadjudicated O/E analysis stratified by age and sex were not statistically significant, except for the total male group, the 0 – 19-year-old male group, the total female group, and the 20 – 29-year-old female group, which all showed a significantly greater observed rate compared to the expected rate.

The AESI of myocarditis and pericarditis has been identified as a confirmed signal and an important identified risk. Further details are provided in Section 16.3.1.1.

15.2.24.2 Pericarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for pericarditis (refer to Appendix 13).

15.2.24.2.1 Results and Discussion

Cases with Nuvaxovid:

Two initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 57 ICSRs were retrieved (28 males, 29 females, age range 23 – 83 years, when reported). The 57 cumulative ICSRs included 57 AEs coded to PT: Pericarditis (n=57). Of the 57 AEs reported, 57 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 57 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 15 hospitalisation, and 2 life-threatening.

Cases with Nuvaxovid XBB.1.5:

One initial and 1 follow-up ICSRs have been retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (3 males, age range 14 – 76 years). The 3 cumulative ICSRs included 3 AEs coded to PT: Pericarditis (n=3). Of the 3 AEs reported, 3 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 3 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

15.2.24.2.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Multiple sets of unadjudicated O/E and sensitivity analyses were generated for pericarditis using the following risk windows; 0 – 7 days, 0 – 14 days, 0 – 30 days, and 0 – 42 days (refer to Table 40 for risk windows).

For the report [redacted], a pericarditis AE with TTO of 25 days was due to auto calculation from the first dose. However, review of the narrative, revealed that this event occurred after the second dose for which partial administration dates were provided. Hence, this AE was accounted for as "missing TTO" in O/E analyses. For the rest of the analysis, this AE will be counted under missing TTO.

Refer to Table 22 for stratification of AEs included in O/E analysis.

Table 22: Stratification of AEs Included in Unadjudicated O/E Analysis for Pericarditis

Parameters	Novavax COVID-19 Vaccines unadjudicated	Nuvaxovid	Nuvaxovid XBB 1.5
Total ICSRs	60	57	3
Total AEs	60	57	3
Number of AEs with TTO reported	38	36	2
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	22	21	1
AEs with TTO falling outside risk windows (All AEs)			
Risk window 0 – 7 days	13	12	1
Risk window 0 – 14 days	4	4	0
Risk window 0 – 30 days	2	2	0
Risk window 0 – 42 days	1	1	0
Total AEs included in O/E analysis (all AEs) stratified by risk window			
Risk window 0 – 7 days	47	45	2
Risk window 0 – 14 days	56	53	3
Risk window 0 – 30 days	58	55	3
Risk window 0 – 42 days	59	56	3
Total AEs included in O/E age and gender stratified analysis (all AEs)			
Risk window 0 – 42 days	59	NA	NA

Risk window 0 – 7 days: When accounting for all formulation cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=47), the unadjudicated

observed rate was significantly greater than expected with an RR of 3.24 (95% CI: 2.38 – 4.31). When assessing by dose formulation for the vaccine, the observed rate was significantly greater than expected for Nuvaxovid (n=45) with an RR of 4.23 (95% CI: 3.08 – 5.66) but lower than expected and not statistically significant for Nuvaxovid XBB.1.5 (n=2).

Risk window 0 – 14 days: When accounting for all formulation cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=56), the unadjudicated observed rate was significantly greater than expected with an RR of 1.93 (95% CI: 1.46 – 2.50). When assessing by dose formulation for the vaccine, the observed rate was significantly greater than expected for Nuvaxovid (n=53) with an RR of 2.49 (95% CI: 1.86 – 3.26), but lower than the expected and not statistically significant for Nuvaxovid XBB.1.5 (n=3).

Risk window 0 – 30 days: When accounting for all formulation cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=58), the unadjudicated observed rate was lower than the expected rate. When assessing by dose formulation for the vaccine, the observed rate was greater than expected but not statistically significant for Nuvaxovid (n=55) and lower than the expected rate for Nuvaxovid XBB.1.5 (n=3).

Risk window 0 – 42 days: When accounting for all formulation cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=59), the unadjudicated observed rate was lower than the expected rate. When assessing by dose formulation for the vaccine, results were similar for Nuvaxovid (n=56) and for Nuvaxovid XBB.1.5 (n=3).

Table 23: Unadjudicated O/E Analysis of Pericarditis with Sensitivity Analysis for All Cumulative AEs

Risk window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
Novavax COVID-19 Vaccines			
0 – 7 Days	3.24 (2.38 – 4.31)*	6.48 (4.76 – 8.61)*	12.95 (9.52 – 17.22)*
0 – 14 Days	1.93 (1.46 – 2.50)*	3.86 (2.91 – 5.01)*	7.71 (5.83 – 10.02)*
0 – 30 Days	0.98 (0.74 – 1.27)	1.96 (1.49 – 2.53)*	3.92 (2.98 – 5.07)*
0 – 42 Days	0.74 (0.56 – 0.95)**	1.47 (1.12 – 1.90)*	2.95 (2.24 – 3.80)*
Nuvaxovid			
0 – 7 Days	4.23 (3.08 – 5.66)*	8.46 (6.17 – 11.31)*	16.91 (12.33 – 22.63)*
0 – 14 Days	2.49 (1.86 – 3.26)*	4.98 (3.73 – 6.51)*	9.96 (7.46 – 13.03)*
0 – 30 Days	1.29 (0.97 – 1.68)	2.58 (1.94 – 3.36)*	5.16 (3.89 – 6.72)*
0 – 42 Days	0.99 (0.74 – 1.28)	1.97 (1.49 – 2.56)*	3.94 (2.98 – 5.12)*

Table 23: Unadjudicated O/E Analysis of Pericarditis with Sensitivity Analysis for All Cumulative AEs

Risk window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
Nuvaxovid XBB.1.5			
0 – 7 Days	0.52 (0.06 – 1.86)	1.03 (0.12 – 3.73)	2.07 (0.25 – 7.46)
0 – 14 Days	0.39 (0.08 – 1.13)	0.77 (0.16 – 2.26)	1.55 (0.32 – 4.53)
0 – 30 Days	0.18 (0.04 – 0.53) **	0.36 (0.07 – 1.06)	0.72 (0.15 – 2.11)
0 – 42 Days	0.13 (0.03 – 0.38) **	0.26 (0.05 – 0.76) **	0.52 (0.11 – 1.51)

* Increased and statistically significant O/E result

** Decreased and statistically significant O/E result

15.2.24.2.2.1 Results of Unadjudicated O/E Analysis Stratified by Age and Sex

When accounting for all formulation cumulative pericarditis AESI reports (n=59), stratified by age and sex with a risk window of 0 – 42 days, the unadjudicated observed rate as reported for the total male group (n=30) and the total female group (n=29) was lower than the expected rate. No statistically significant increased O/E was observed.

Table 24: Unadjudicated O/E Analysis of Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	1	4.17 (0.13 – 23.24)	0	0 (0 – 17.88)
20 – 39	15	1.35 (0.76 – 2.23)	12	1.45 (0.75 – 2.53)
40 – 59	9	0.61 (0.28 – 1.15)	12	0.95 (0.49 – 1.66)
60+	2	0.18 (0.02 – 0.65) **	5	0.44 (0.14 – 1.04)
Missing	3	N/A	0	N/A
Total	30	0.82 (0.55 – 1.17)	29	0.86 (0.57 – 1.23)

** Decreased and statistically significant O/E results.

15.2.24.2.2.2 Limitations to O/E Analysis Stratified by Age and Sex

Demographic information on age and sex was only available in exposure data from Australia, EU, Switzerland, Japan, UK and New Zealand, and none of the countries reported the exposure data in the age categories requested. In addition, only UK provides data on patient sex. As proposed by Mahaux 2016, the demographic distributions of the observed reports could be used to approximate the missing demographic distributions in exposure data. Therefore, the proportion of the observed count of reports (including all AEs) received from a given strata compared to the total count of reports received was applied to the exposure data to

get the stratum-specific exposure data currently. However, this methodology may lead to substantially biased distributions of the exposure across strata due to differential reporting rates across ages and sexes. Additionally, age- and sex-related differences in spontaneous reporting rates following immunisation (including COVID-19 immunisation) are well documented in the literature [Xiong 2021]. In summary, the current available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable.

15.2.24.2.3 Conclusion

The unadjudicated O/E showed a greater than expected observed rate that was statistically significant for 0 – 7 and 0 – 14-day risk windows overall and for Nuvaxovid. No increase was observed with Nuvaxovid XBB.1.5. Results of the unadjudicated O/E analysis stratified by age and sex were not increased and statistically significant.

The AESI of myocarditis and pericarditis has been identified as a confirmed signal. Further details are provided in Section 16.3.1.1.

15.2.24.3 Myocarditis and Pericarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for myocarditis and pericarditis (refer to Appendix 13).

15.2.24.3.1 Results and Discussion

Cases with Nuvaxovid:

Two initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 89 ICSRs were retrieved (42 males, 47 females, age range 18 – 83 years, when reported). The 89 cumulative ICSRs included 91 AEs coded to PTs: Pericarditis (n=57), Myocarditis (n=24), Myopericarditis (n=7), and Carditis (n=3). Of the 91 AEs reported, 91 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 91 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 24 hospitalization, and 2 life-threatening.

Cases with Nuvaxovid XBB.1.5:

Four initial and 1 follow-up ICSRs have been retrieved for the current reporting interval.

Cumulatively, 6 ICSRs were retrieved (3 males, 2 females, 1 individual of unknown sex, age range 14 – 76 years, when reported). The 6 cumulative ICSRs included 6 AEs coded to PTs: Pericarditis (n=3), Myopericarditis (n=1), Carditis (n=1), and Myocarditis (n=1). Of the 6 AEs reported, 6 were serious, with the events meeting the following criteria: 6 medically

significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

15.2.24.3.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Multiple sets unadjudicated O/E and sensitivity analyses were generated for myocarditis and pericarditis using the following risk windows: 0 – 7 days, 0 – 14 days, 0 – 30 days, and 0 – 42 days (refer to Table 40 for risk windows).

For the report [redacted], pericarditis AE with TTO of 25 days appeared due to database's auto calculation from first dose. However, upon review of the narrative, it was identified that the event occurred after the second dose for which partial administration dates were provided. Hence this AE was accounted for as "missing TTO" in O/E analyses. For the rest of the analysis, this AE will be counted under "missing TTO". Additionally, two reports contained two AEs coded to PTs Pericarditis and Myocarditis which reportedly occurred on the same day and hence each were pooled as one report for the O/E analysis.

Refer to Table 25 for stratification of AEs included in O/E analysis.

Table 25: Stratification of AEs Included in Unadjudicated O/E Analysis for Myocarditis and Pericarditis

Parameters	Novavax COVID-19 Vaccines unadjudicated	Nuvaxovid	Nuvaxovid XBB 1.5
Total ICSRs	95	89	6
Total AEs	97	91	6
Number of AEs with TTO reported	61	59	3
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	36	33	3
AEs with TTO falling outside risk windows			
Risk window 0 – 7 days	20	19	1
Risk window 0 – 14 days	9	9	0
Risk window 0 – 30 days	4	4	0
Risk window 0 – 42 days	3	3	0
Total AEs included in O/E analysis stratified by risk window			
Risk window 0 – 7 days	75	70	5
Risk window 0 – 14 days	86	80	6
Risk window 0 – 30 days	91	85	6
Risk window 0 – 42 days	92	86	6

Table 25: Stratification of AEs Included in Unadjudicated O/E Analysis for Myocarditis and Pericarditis

Total AEs included in O/E age and gender stratified analysis			
Risk window 0 – 42 days	92	NA	NA

Risk window 0 – 7 days: When accounting for all formulation cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=75), the unadjudicated observed rate was significantly greater than expected with an RR of 4.25 (95% CI: 3.34 – 5.32). When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=70) with an RR of 5.52 (95% CI: 4.31 – 6.98) but no different from expected for Nuvaxovid XBB.1.5 (n=5).

Risk window 0 – 14 days: When accounting for all formulation cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=86), the unadjudicated observed rate was significantly greater than expected with an RR of 2.43 (95% CI: 1.95 – 3.01). When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=80) with an RR of 3.16 (95% CI: 2.50 – 3.93) but lower than expected for Nuvaxovid XBB.1.5 (n=6).

Risk window 0 – 30 days: When accounting for all formulation cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=91), the unadjudicated observed rate was significantly greater than expected with an RR of 1.27 (95% CI: 1.02 – 1.55). When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=85) with an RR of 1.68 (95% CI: 1.34 – 2.08) but lower than expected for Nuvaxovid XBB.1.5 (n=6).

Risk window 0 – 42 days: When accounting for all formulation cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=92), the unadjudicated observed rate was lower than expected rate. When assessing by dose formulation for the vaccine, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=86) with an RR of 1.28 (95% CI: 1.02 – 1.58) but lower than expected for Nuvaxovid XBB.1.5 (n=6).

Table 26: Unadjudicated O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

Risk Window	**O/E Rate Ratio (95% CI)**	**Assuming 50% Underreporting**	**Assuming 75% Underreporting**
Novavax COVID-19 Vaccines			
0 – 7 Days	4.25 (3.34 – 5.32) *	8.50 (6.68 – 10.65) *	16.99 (13.37 – 21.30) *
0 – 14 Days	2.43 (1.95 – 3.01) *	4.87 (3.90 – 6.01) *	9.74 (7.79– 12.03) *
0 – 30 Days	1.27 (1.02 – 1.55) *	2.53 (2.04 – 3.11) *	5.06 (4.08 – 6.22) *
0 – 42 Days	0.95 (0.76 – 1.16)	1.89 (1.53 – 2.32) *	3.79 (3.05 – 4.65) *

Table 26: Unadjudicated O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

Nuvaxovid			
0 – 7 Days	5.52 (4.31 – 6.98) *	11.05 (8.61 – 13.96) *	22.10 (17.23 – 27.92) *
0 – 14 Days	3.16 (2.50 – 3.93) *	6.31 (5.01 – 7.86) *	12.63 (10.01 – 15.72) *
0 – 30 Days	1.68 (1.34 – 2.08) *	3.36 (2.69 – 4.16) *	6.73 (5.37 – 8.32) *
0 – 42 Days	1.28 (1.02 – 1.58) *	2.56 (2.05 – 3.16) *	5.12 (4.09 – 6.32) *
Nuvaxovid XBB.1.5			
0 – 7 Days	1.00 (0.32 – 2.34)	2.00 (0.65 – 4.68)	4.01 (1.30 – 9.36) *
0 – 14 Days	0.60 (0.22 – 1.31)	1.20 (0.44 – 2.62)	2.41 (0.88 – 5.24)
0 – 30 Days	0.28 (0.10 – 0.61) **	0.56 (0.21 – 1.22)	1.12 (0.41– 2.44)
0 – 42 Days	0.20 (0.07 – 0.44) **	0.40 (0.15 – 0.87) **	0.80 (0.29 – 1.75)

* Increased and statistically significant O/E results.

** Decreased and statistically significant O/E results.

15.2.24.3.2.1 Results of Unadjudicated O/E Analysis Stratified by Age and Sex

When accounting for all formulation cumulative myocarditis and pericarditis reports with a risk window of 0 – 42 days (n=92), stratified by age and sex, the unadjudicated observed rate was significantly greater than expected in the 0 – 19-year-old male group (n=4) with an RR of 9.01 (95% CI: 2.45 – 23.06) and in the 20 – 29-year-old male group (n=13) with an RR of 2.88 (95% CI: 1.53 – 4.93). The unadjudicated observed rate in total female group (n=48), was significantly greater than expected with an RR of 1.53 (95% CI: 1.13 – 2.03). Significantly greater than expected unadjudicated observed rates were found in the 20 – 29-year-old female group (n=11) with an RR of 5.57 (95% CI: 2.78 – 9.96), in the 30 – 39-year-old female group (n=10) with an RR of 2.22 (95% CI: 1.06 – 4.07), and in the 40 – 49-year-old female group (n=13) with an RR of 2.26 (95% CI: 1.20 – 3.86).

Table 27: Unadjudicated O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	4	9.01 (2.45 – 23.06) *	0	0 (0 – 35.26)
20 – 29	13	2.88 (1.53 – 4.93) *	11	5.57 (2.78 – 9.96) *
30 – 39	7	1.10 (0.44 – 2.27)	10	2.22 (1.06 – 4.07) *
40 – 49	8	1.46 (0.63 – 2.88)	13	2.26 (1.20 – 3.86) *
50 – 59	5	0.88 (0.29 – 2.06)	6	0.81 (0.30 – 1.76)
60 – 69	0	0 (0 – 0.69)	5	0.82 (0.26 – 1.90)
70 – 79	1	0.26 (<0.01 – 1.47)	1	0.25 (<0.01 – 1.41)

Table 27: Unadjudicated O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	4	9.01 (2.45 – 23.06) *	0	0 (0 – 35.26)
20 – 29	13	2.88 (1.53 – 4.93) *	11	5.57 (2.78 – 9.96) *
80+	1	0.74 (0.02 – 4.13)	0	0 (0 – 2.44)
Missing	4	N/A	2	N/A
Total	43	1.30 (0.94 – 1.76)	48	1.53 (1.13 – 2.03) *

* Increased and statistically significant O/E results.

15.2.24.3.2.2 Limitations to O/E Analysis Stratified by Age and Sex

Demographic information on age and sex was only available in exposure data from Australia, EU, Switzerland, Japan, UK and New Zealand, and none of the countries reported the exposure data in the age categories requested. In addition, only UK provides exposure data on patient sex. As proposed by Mahaux 2016, the demographic distributions of the observed reports could be used to approximate the missing demographic distributions in exposure data. Therefore, the proportion of the observed count of reports received from a given strata compared to the total count of reports received was applied to the exposure data to get the stratum-specific exposure data currently. However, this methodology may lead to substantially biased distributions of the exposure across strata due to differential reporting rates across ages and sexes. Additionally, age- and sex-related differences in spontaneous reporting rates following immunisation (including COVID-19 immunisation) are well documented in the literature [Xiong 2021]. In summary, the current available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable.

15.2.24.3.3 Conclusion

Overall, the unadjudicated O/E results for cumulative myocarditis and pericarditis showed an increased observed rate that was statistically significant for 0 – 7, 0 – 14 and 0 – 30 days risk windows. For Nuvaxovid, the unadjudicated O/E result for cumulative myocarditis and pericarditis also showed a significantly greater than expected observed rate for the 0 – 42 days risk windows.

The unadjudicated O/E result for all reports stratified by age and sex revealed an increased observed rate that was statistically significant in the 0 – 29-year-old male group, the total female group, and the 20 – 49-year-old female group.

The AESI of myocarditis and pericarditis underwent a complete signal evaluation and was identified as a confirmed signal and an important identified risk. Further details and analysis are provided in Section 16.3.1.1. Events of myocarditis and pericarditis will continue to be monitored across both narrow (included in O/E analyses) and broad search strategies for changes in characteristics of the events and for the identification of potential risk factors.

15.2.25 Narcolepsy

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for narcolepsy (refer to Appendix 13).

15.2.25.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.26 Neonatal Death

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for neonatal death (refer to Appendix 13).

15.2.26.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.27 Oculomotor Cranial Nerve Disorders

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for oculomotor cranial nerve disorders (refer to Appendix 13).

15.2.27.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 females, 72 years). The 1 cumulative ICSR included 1 serious AE coded to PT: IIIrd nerve paralysis (n=1), with the event meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria).

15.2.27.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO was reported as 6 days for this single report, which fell within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid and O/E analysis for Nuvaxovid XBB.1.5 (n=1) remained similar to all formulation O/E analysis.

15.2.27.3 Conclusion

The single ICSR met TTO inclusion criteria and results of unadjudicated O/E and sensitivity analyses showed lower than expected rates.

No safety signal was identified.

15.2.28 Optic Neuritis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for optic neuritis (refer to Appendix 13).

15.2.28.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, age 37 years). This single cumulative ICSR included 1 AE coded to PT Optic neuritis. This AE was serious, meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria).

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.28.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for this single AE was reported as 10 days, which fell within the risk window of 0 – 42 days (refer to Table 40). O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were reported for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=1) remained similar to all formulation O/E analysis.

15.2.28.3 Conclusion

A single ICSR met the TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.29 Postural Orthostatic Tachycardia Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for postural orthostatic tachycardia syndrome (refer to Appendix 13).

15.2.29.1 Results and Discussion

Cases with Nuvaxovid:

One initial and 1 follow-up ICSR was retrieved for the current reporting interval. The follow-up case included an additional PT that qualified the ICSR for this interval.

Cumulatively, 5 ICSRs were retrieved (2 male, 3 females, age range 26 – 50 years). The 5 cumulative ICSRs included 5 AEs coded to PT: Postural orthostatic tachycardia syndrome (n=5). Of the 5 AEs reported, 2 were serious, with the event meeting the following criteria: 1 medically significant (based on medical judgement) and 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, age 42 years). The 1 ICSR included 1 serious AE coded to PT: Postural orthostatic tachycardia syndrome (n=1), with the event meeting the following criteria: 1 medically significant (based on medical judgement) and 1 disability.

15.2.29.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for 3 out of 6 AEs was reported as 0, 3, and 4 days, which fell within the risk window of 0 – 42 days (refer to Table 40). TTO was not reported for the other 3 AEs, and they were conservatively assumed to fall within the risk window of 0 – 42 days. Therefore, all AEs met the inclusion criteria for the observed count (n=6). O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=5) and Nuvaxovid XBB.1.5 (n=1) remained similar to all formulation O/E analysis.

15.2.29.3 Conclusion

Six ICSRs met inclusion criteria for observed count and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.30 Pre-eclampsia

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for pre-eclampsia (refer to Appendix 13).

15.2.30.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, ages 35 years and 38 years). The 2 cumulative ICSRs included 3 AEs coded to PTs: Pre-eclampsia (n=2) and Gestational hypertension (n=1). Of the 3 AEs reported, 2 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, age 35 years). The ICSR included 1 non-serious AE coded to PT: Gestational hypertension (n=1).

15.2.30.2 Results of Unadjudicated O/E Analysis

O/E analysis was not performed for pre-eclampsia due to the inability to accurately determine exposure only in pregnant females and an indeterminate risk window.

15.2.30.3 Conclusion

No safety signal was identified.

15.2.31 Preterm Birth

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for rheumatoid arthritis (refer to Appendix 13).

15.2.31.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 linked (maternal and neonate) ICSRs were retrieved (1 female 35 years, 1 male neonate, unknown age). The maternal ICSR included 1 AE coded to PT: Premature delivery and the neonate ICSR included 1 AE coded to PT: Premature baby. Both AEs were non-serious.

Cases with Nuvaxovid XBB.1.5:

One initial and 1 follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 2 linked (maternal and neonate) ICSRs were retrieved (1 female 36 years, 1 female neonate, unknown age). The maternal ICSR included 1 AE coded to PT: Premature delivery and the neonate ICSR included 1 AE coded to PT: Premature baby. Both AEs were non-serious.

15.2.31.2 Results of the O/E Analysis

O/E analysis was not performed for preterm birth due to the inability to accurately determine exposure only in pregnant females and an indeterminate risk window.

15.2.31.3 Conclusion

No safety signal was identified.

15.2.32 Rheumatoid Arthritis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for rheumatoid arthritis (refer to Appendix 13).

15.2.32.1 Results and Discussion

Cases Nuvaxovid:

One initial and 1 follow-up ICSRs have been retrieved for the current reporting interval.

Cumulatively, 8 ICSRs were retrieved (4 males, 4 females, age range 29 – 74 years, when reported). The 8 cumulative ICSRs included 8 AEs coded to PTs: Rheumatoid arthritis (n=6), Polyarthritis (n=1), and Rheumatoid lung (n=1). Of the 8 AEs reported, 8 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 7 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 2 hospitalization, and 1 death.

Cases with Nuvaxovid XBB.1.5:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, 54 years). The 1 cumulative ICSR included 1 serious AE coded to PT: Polyarthritis (n=1), with the event meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria).

15.2.32.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for 4 of 9 AEs ranged from 0 – 33 days, which fell within the risk window of 0 – 42 days (refer to Table 40). The TTO was not reported for 3 AEs, which were conservatively included in O/E analyses. TTO for 2 AEs fell outside the risk window of 0 – 42 days. Therefore, 7 of 9 AEs met the inclusion criteria for the observed count (n=7). The O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=6) and Nuvaxovid XBB.1.5 (n=1) remained similar to all formulation O/E analysis.

15.2.32.3 Conclusion

Seven ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.33 Spontaneous Abortion

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for spontaneous abortion (refer to Appendix 13).

15.2.33.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (4 females, age range 23 – 31 years). The 4 cumulative ICSRs included 4 AEs coded to PT: Abortion spontaneous. Of the 4 AEs reported, 4 were serious, with the events meeting the following criteria: 4 medically significant (based on medical judgement or serious by convention, meeting IME criteria).

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, age 32 years). The 1 ICSR included 1 serious AE coded to PT: Abortion spontaneous meeting the following criteria: 1 medically significant (based on medical judgement or serious by convention, meeting IME criteria).

15.2.33.2 Results of the O/E Analysis

No O/E analysis could be performed for spontaneous abortion, due to the inability to accurately determine exposure only in pregnant females.

15.2.33.3 Conclusion

No safety signal was identified.

15.2.34 Stillbirth

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for stillbirth (refer to Appendix 13).

15.2.34.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

15.2.35 Sudden Death

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for sudden death (refer to Appendix 13).

15.2.35.1 Results and Discussion

Cases with Nuvaxovid:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 male, 54 years). The 1 cumulative ICSR included 1 AE coded to PT: Sudden death, which was serious due to meeting the following criteria (an event may meet more than one seriousness criterion): medically significant (based on medical judgement or serious by convention, meeting IME criteria) and death.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, 91 years). The 1 cumulative ICSR included 1 AE coded to PT: Sudden death, which was serious due to meeting the following criteria (an event may meet more than one seriousness criterion): medically significant (based on medical judgement or serious by convention, meeting IME criteria) and death.

15.2.35.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for the 2 sudden deaths were 1 and 25 days, which fell within the risk window of 0 – 60 days (refer to Table 40). Therefore, 2 of 2 events met the inclusion criteria for the observed count (n=2). The O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=1) and Nuvaxovid XBB.1.5 (n=1) remained similar to the all formulation O/E analysis.

15.2.35.3 Conclusion

No safety signal was identified.

15.2.36 Thrombocytopenia

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for thrombocytopenia (refer to Appendix 13).

15.2.36.1 Results and Discussion

Cases with Nuvaxovid:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 9 ICSRs were retrieved (1 male 8 females, age range 23 – 78 years, when reported). The 9 cumulative ICSRs included 10 AEs coded to PTs: Thrombocytopenia (n=5), Immune thrombocytopenia (n=4) and Thrombosis with thrombocytopenia syndrome (n=1). All 10 reported AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 10 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 3 hospitalisation.

Of note, the ICSR with PT: Thrombosis with thrombocytopenia syndrome was also retrieved by the search strategy for the AESI, Thrombosis with thrombocytopenia syndrome (Section 15.2.37).

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.36.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Nine ICSRs were reported for Thrombocytopenia. One of the reports contained 2 AEs coded to PTs Immune thrombocytopenia and Thrombocytopenia which reportedly occurred on the same day and hence were pooled into 1 report for the O/E analysis. Therefore, after pooling 2 AEs into 1 case, 9 AEs were considered for O/E analysis. The TTO for 4 of the 9 AEs being considered for O/E analysis ranged from 6 – 34 days which, were within the risk window of 0 – 42 days (refer to Table 40). TTO was not reported in the other 5 AEs, which were conservatively included in O/E analyses. Therefore, 9 AEs met inclusion criteria for the observed count (n=9) for O/E analysis. For all formulation, the unadjudicated O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were identified for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=9) remained similar to the all formulation O/E analysis.

15.2.36.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.37 Thrombosis with Thrombocytopenia Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for thrombosis with thrombocytopenia syndrome (refer to Appendix 13).

15.2.37.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, 69 years) and included 1 AE coded to the PT of Thrombosis with thrombocytopenia syndrome (n=1) which was serious meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria) and hospitalisation.

Of note, this ICSR also was retrieved by the search strategy for thrombocytopenia (Section 15.2.36).

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.37.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for this single report was 6 days, which fell within the risk window of 0 – 28 days (refer to Table 40). O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, no cases were identified for Nuvaxovid XBB.1.5 and O/E analysis for Nuvaxovid (n=1) remained similar to all formulation O/E analysis.

15.2.37.3 Conclusion

The single ICSR met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.38 Transverse Myelitis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for transverse myelitis (refer to Appendix 13).

15.2.38.1 Results and Discussion

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, 54 years). The 1 cumulative ICSR included 1 AE coded to PT: Myelitis transverse. The AE was serious meeting the following criteria: medically significant (meeting IME criteria) and hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, 27 years). The 1 cumulative ICSR included 1 AE coded to PT Poliomyelitis. The AE was serious meeting the following criteria: medically significant (meeting IME criteria).

15.2.38.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO for one AE was reported as 11 days while TTO for the second AE was not reported and was conservatively included in O/E analyses. O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=1) and Nuvaxovid XBB.1.5 (n=1) remained similar to all formulation O/E analysis.

15.2.38.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.39 Vaccine Associated Enhanced Disease

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for vaccine associated enhanced disease (refer to Appendix 13).

15.2.39.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 7 ICSRs were retrieved (6 males, 1 female, age range 33 – 71 years). The 7 cumulative ICSRs included 7 AEs coded to PT Antibody-dependent enhancement (n=7). All 7 reported AEs were serious, with the events meeting the following criteria: 7 medically significant (based on medical judgement or serious by convention, meeting IME criteria).

Cases with Nuvaxovid XBB.1.5:

No ICSRs were retrieved either cumulatively or for the current reporting interval.

15.2.39.2 Results of Unadjudicated O/E Analysis

O/E analyses was not performed for vaccine associated enhanced disease, as it is not possible to determine an expected rate for this AE, given that vaccine exposure is necessary to develop the condition.

15.2.39.3 Conclusion

No safety signal was identified.

15.2.40 Venous Thromboembolism

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for venous thromboembolism (refer to Appendix 13).

15.2.40.1 Results and Discussion

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 23 ICSRs were retrieved (10 males, 13 females, age range 26 – 85 years, when reported). The 23 cumulative ICSRs included 27 AEs coded to PTs: Pulmonary embolism (n=13), Thrombophlebitis (n=4), Deep vein thrombosis (n=4), Venous thrombosis (n=3), Superficial vein thrombosis (n=2), and Cerebral venous sinus thrombosis (n=1). Of the 27 AEs reported, 22 were serious, with the events meeting the following criteria (an event may

meet more than one seriousness criterion): 20 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 13 hospitalisation, 5 life-threatening, and 1 disability.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (1 male, 1 female, 65 and 76 years, respectively) and included 2 serious AEs coded to PTs: Deep Vein Thrombosis (n=1) and Pulmonary Embolism (n=1), both meeting the medically significant (based on medical judgement or serious by convention, meeting IME criteria) seriousness criterion.

15.2.40.2 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Two ICSRs contained 2 AEs with the same TTO, hence were pooled into 1 report for the O/E analyses. Therefore, after pooling 2 AEs into 1 case for 2 reports, 25 AEs were considered for O/E analysis for the risk window of 0 – 28 days (refer to Table 40). The TTO for 19 of the 25 AEs ranged from 1 – 28 days. TTO was not reported for 1 AE and was conservatively included for the observed count. The TTO for the other 5 AEs fell outside the risk window. Therefore, 20 AEs met the inclusion criteria for the observed count (n=20) for O/E analyses. For all formulation, the unadjudicated O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=18) and Nuvaxovid XBB.1.5 (n=2) remained similar to all formulation O/E analysis.

15.2.40.3 Conclusion

Twenty AEs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.3 Additional Safety Topics for Monitoring

The global vaccine safety database was queried for the cumulative period up to 19-Jun-2024 according to the prespecified search strategies for the safety topics listed below (refer to Appendix 14 for search strategy of safety topics).

- Death, All Cause (refer to Section 15.3.1)
- Cholecystitis (refer to Section 15.3.2)
- Diarrhoea (refer to Section15.3.3)

- Herpes Zoster (refer to Section 15.3.4)
- Inflammatory eye disorders (refer to Section 15.3.5)
- Menstrual disorders (refer to Section 15.3.6)
- Paraesthesia (refer to Section 15.3.7)
- Reactogenicity profile- second dose and boosters (based on impurity levels) (refer to Section 15.3.8)
- Review of safety concerns in elderly and off-label paediatric use (refer to Section 15.3.9)
- Tinnitus (refer to Section 15.3.10)
- Vaccine anxiety-related reactions (refer to Section 15.3.11)
- Vaccination failures / lack of efficacy (refer to Section 15.3.12)

15.3.1 Death, All Cause

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for death, all cause (refer to Appendix 14).

Cases with Nuvaxovid:

One initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 34 ICSRs were retrieved (20 males, 14 females, age range 13 – 96 years, when reported). The 34 cumulative ICSRs included 59 fatal AEs coded to PTs (n>1) Death (n=14), Dyspnoea (n=4), Pyrexia (n=3), Adverse event following immunisation (n=2), Cerebrovascular accident (n=2), Dizziness (n=2), and Headache (n=2). Additional co-reported non-fatal PTs are included in the line listing.

Cases with Nuvaxovid XBB.1.5:

Seven initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 8 ICSRs were retrieved (2 males, 6 females, age range 77 – 94 years, when reported). The 8 cumulative ICSRs included 21 fatal AEs coded to PTs (n>1): Death (n=5), Asthenia (n=2), and Pyrexia (n=2). Additional co-reported non-fatal PTs are included in the line listing.

Appendix 20 includes interval line listing of fatal cases received as of the DLP (19-Jun-2024).

15.3.1.1 Results of O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

For all formulation O/E analysis, TTO in 32 of 41 reports considered for O/E analysis with fatal outcome ranged from 0 – 60 days, which fell within the risk window of 0 – 60 days (refer to Table 40). Three reports with fatal outcome fell outside the risk window and were excluded from the O/E. TTO was not reported for the other 6 reports, and these were conservatively included as falling within the risk window. Therefore, 38 of 41 reports met inclusion criteria for O/E (n=38) and the results showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, O/E analysis for Nuvaxovid (n=30) and Nuvaxovid XBB.1.5 (n=8) remained similar to all formulation O/E analysis.

15.3.1.2 Conclusion

Thirty-eight ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates.

No safety signal was identified.

15.3.2 Cholecystitis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for cholecystitis (refer to Appendix 14).

Cases with Nuvaxovid:

One follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 9 ICSRs were retrieved (3 males, 6 females, age range 38 – 84 years, when reported). The 9 cumulative ICSRs included 9 AEs coded to PTs Abnormal faeces (n=4), Jaundice (n=2), Blood bilirubin increased (n=1), Faeces pale (n=1) and Gallbladder disorder (n=1). Of the 9 AEs reported, 3 AEs were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (gender and age was not provided). The ICSR included 1 nonserious AE coded to PT Abnormal faeces (n=1).

No safety signal was identified.

15.3.3 Diarrhoea

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for diarrhoea (refer to Appendix 14).

Cases with Nuvaxovid:

Two initial and 4 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 137 ICSRs were retrieved (27 males, 110 females, age range 18 – 86 years, when reported). The 137 cumulative ICSRs included 138 AEs coded to the PT of Diarrhoea. Of the 138 AEs reported, 23 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 11 medically significant (based on medical judgement), 12 hospitalisation, and 2 disability.

Cases with Nuvaxovid XBB.1.5:

Four initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 7 ICSRs were retrieved (4 males, 3 females, age range 31 - 92 years, when reported). The 7 cumulative ICSRs included 7 AEs coded to PT of Diarrhoea. Of the 7 AEs reported, 1 was serious, with the event meeting the following criteria: hospitalisation.

No safety signal was identified.

15.3.4 Herpes Zoster

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for Herpes Zoster (refer to Appendix 14).

Cases with Nuvaxovid:

No ICSRs have been retrieved for the current reporting interval.

Cumulatively, 40 ICSRs were retrieved (11 males, 28 females, 1 individual of unknown sex, age range 24 – 76 years, when reported). The 40 cumulative ICSRs included 42 AEs coded to PTs Herpes zoster (n=38), Herpes zoster meningoencephalitis (n=1), Herpes zoster oticus (n=1), Herpes zoster reactivation (n=1), and Ophthalmic herpes zoster (n=1). Of the 42 AEs reported, 5 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 4 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 3 hospitalisation, and 1 life-threatening.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, age 41 years). The ICSR included 1 non-serious AE coded to PT Herpes zoster (n=1).

15.3.4.1 Results of Unadjudicated O/E Analysis

An all-Novavax COVID-19 O/E analysis was performed in addition to formulation-specific O/E analyses.

Parallel sets of O/E and sensitivity analyses were generated for Herpes Zoster using the following risk windows; 0 – 7 days, 0 – 14 days, 0 – 30 days and 0 – 42 days. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate for all risk windows.

15.3.4.2 Conclusion

No safety signal was identified.

15.3.5 Inflammatory Eye Disorders

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for inflammatory eye disorders (refer to Appendix 14). During the current reporting interval, the search strategy for this safety topic (with an HLT/HLGT based search strategy) was expanded to include selected PTs that map to the specific HLT/HLGT through their secondary SOC.

Cases with Nuvaxovid:

One initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 66 ICSRs were retrieved (13 males, 53 females, age range 16 – 72 years, when reported). These 66 cumulative ICSRs included 78 AEs. The most frequently reported AEs (n≥4) were coded to PTs Eye swelling (n=17), Photophobia (n=10), Ocular hyperaemia (n=9), Diplopia (n=6), Lacrimation increased (n=6), Swelling of eyelid (n=5), Eye inflammation (n=5), Eyelid oedema (n=4) and Eye irritation (n=4). Of the 78 AEs reported, 13 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 9 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 4 hospitalization, 1 life-threatening and 1 disability.

Cases with Nuvaxovid XBB.1.5:

One initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (2 males, 2 female, age range 31 – 78 years). These 4 cumulative ICSRs included 5 AEs coded to PTs Conjunctivitis (n=1), Diplopia (n=1), Eye irritation (n=1), Lacrimation increased (n=1), and Photophobia (n=1). Of the 5 AEs reported, 1 was serious, with the event meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria).

No safety signal was identified.

15.3.6 Menstrual Disorders

The safety topic of menstrual disorders became a validated signal on 27-Jun-2022. As of 05-Aug-2022, this signal has been refuted and the topic is being monitored via routine pharmacovigilance activities.

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for menstrual disorders (refer to Appendix 14).

Cases with Nuvaxovid:

Two initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 138 ICSRs were retrieved (138 females, age range 20 – 73 years, when reported). The 138 cumulative ICSRs included 209 AEs. The most frequently reported AEs (n>15) were coded to PTs Menstrual disorder (n=50), Heavy menstrual bleeding (n=39), Abnormal uterine bleeding (n=23), Dysmenorrhoea (n=20), Menstruation irregular (n=18), and Amenorrhoea (n=16). Of the 209 AEs, 10 AEs were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 8 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

No safety signal was identified.

15.3.6.1 Results of Menstrual Disorders Rechallenge

During this reporting interval, there were no new positive re-challenge cases.

15.3.7 Paraesthesia

This safety topic of paraesthesia was designated as a validated signal on 27-May-2022, underwent complete signal evaluation and was confirmed as signal on 27-Jun-2022. Paraesthesia was added to the CCDS in Section 4.8 (Undesirable Effects).

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for paraesthesia (refer to Appendix 14). During the current reporting interval, the search strategy for this safety topic (which is HLT/HLGT based) was expanded to include selected PTs that map to that HLT/HLGT through their secondary SOC.

Cases with Nuvaxovid:

Six initial and 8 follow-up ICSRs were retrieved during the current reporting interval.

Cumulatively, 415 ICSRs were retrieved (108 males, 305 females, 2 individuals of unspecified sex, age range 13 – 81 years, when reported). The 415 cumulative ICSRs included 514 AEs coded to PTs Paraesthesia (n=308), Hypoaesthesia (n=136), Burning sensation (n=38), Skin burning sensation (n=14), and Hyperaesthesia (n=8), Dysaesthesia (n=8), and Hemiparaesthesia (n=2). Of the 514 AEs reported, 73 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 44 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 26 hospitalisation, and 6 disability.

Cases with Nuvaxovid XBB.1.5:

Nine initial ICSRs were retrieved during the current reporting interval.

Cumulatively, 19 ICSRs were retrieved (4 males, 15 females, age range 28 – 77 years, when reported). The 19 cumulative ICSRs included 25 AEs coded to PTs Paraesthesia (n=15), Hypoaesthesia (n=8), Skin burning sensation (n=1), and Dysaesthesia (n=1). Of the 25 AEs reported, 5 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 4 hospitalisation, and 1 disability.

No significant safety information was received during the reporting interval that would alter previously known information for this confirmed signal. This topic will continue to be monitored for further characterisation of the risk, via routine pharmacovigilance activities.

15.3.8 Reactogenicity Profile-Second Dose and Boosters (Based on Impurity Levels)

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for reactogenicity profile-second dose and boosters (refer to Appendix 14). During the current reporting interval, the search for this safety topic utilized a newly configured report, in conjunction with implementation of the new NVX Global Safety Database, which included a filter for second and booster doses and did not include a filter for available lot numbers. For the current interval, reports lacking lot numbers were pulled into the search strategy, explaining the notable increase in total number of ICSRs received for this safety topic. Upon review of the ICSRs retrieved, no safety signal was identified.

Cases with Nuvaxovid:

Seven initial and 22 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 317 ICSRs were retrieved (88 males, 217 females, 12 individuals of unspecified sex, age range 12 – 93 years, when reported), of which 144 ICSRs contained lot numbers. The 317 cumulative ICSRs included 852 AEs, with the most frequently reported PTs ($n \geq 50$): Headache (n=123), Fatigue (n=118), Injection site pain (n=84), Pyrexia (n=83), Myalgia (n=55), Malaise (n=53), and Nausea (n=50). Of the 852 AEs, 121 AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 38 medically significant (based on medical judgement or serious by convention,

meeting IME criteria), 45 hospitalisation, 5 life threatening, 54 disability and 3 Death. The number of ICSRs reporting events meeting the seriousness criteria of hospitalisation (n=45 AEs) and disability (n=54 AEs), were 21 and 12, respectively. Review of these ICSRs did not identify any safety concerns.

No trends related to reactogenicity based on impurity levels specifically after a second dose and/or a booster were identified.

Cases with Nuvaxovid XBB.1.5:

Six initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 9 ICSRs were retrieved (2 males, 5 females, and 2 individuals of unspecified sex, age range 35 – 80 years, when reported), of which 5 ICSRs contained a lot number. The 9 cumulative ICSRs included 20 non-serious AEs coded to Vaccination site pain (n=4), Fatigue (n=4), Headache (n=1), Injection site discolouration (n=1), Injection site erythema (n=1), Injection site mass (n=1), Injection site pruritus (n=1), Muscular weakness (n=1), Myalgia (n=1), Pyrexia (n=1), Vaccination site erythema (n=1), Vaccination site induration (n=1), Vaccination site mass (n=1), and Vaccination site swelling (n=1).

No trends related to reactogenicity based on impurity levels specifically after a second dose and/or a booster were identified.

No safety signal was identified.

15.3.9 Review of Safety Concerns in Elderly and Off-label Paediatric Use

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategies for review of safety concerns in elderly and off-label paediatric use (refer to Appendix 14). The search strategy for off-label paediatric use was updated during the interval, to remove the age group: Foetus. Foetal information is included under section Foetal and neonate ICSRs (Section 16.3.5.1.2).

15.3.9.1 Review of Safety Concerns in Elderly

Cases with Nuvaxovid:

Twenty-two initial and 7 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 729 ICSRs were retrieved (254 males, 468 females, 7 individuals of unknown sex, age range 65 – 96 years, when reported). These 729 ICSRs included 2126 AEs. The 5 most frequently reported AEs were coded to PTs Myalgia (n=137), Headache (n=115), Dizziness (n=87), Hypersensitivity (n=80), and Injection site pain (n=62). Of the 2,126 AEs, 441 AEs were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 264 medically significant (based on medical judgement or serious by

convention, meeting IME criteria), 208 hospitalisation, 64 disability, 7 life-threatening and 43 fatal AEs.

Cases with Nuvaxovid XBB.1.5:

Sixty-one initial and 4 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 97 ICSRs were retrieved (39 males, 57 females, 1 individual of unspecified age, age range 65 – 94 years). The 97 cumulative ICSRs included 369 AEs coded to PTs (n≥10): Headache (n=14), Pyrexia (n=13), Pain in extremity (n=13), Fatigue (n=11), Dizziness (n=10), Expired product administered (n=10), and Product storage error (n=10). Of the 369 AEs reported, 72 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 41 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 25 hospitalisation, 7 disability, 1 life-threatening and 20 fatal AEs.

Disproportionate reporting of expired product administered is reviewed in Section 9.2. All other reports are consistent with the general AE profile as defined in the CCDS for the overall population.

Safety data in the elderly are consistent with the overall safety profile. No safety signal was identified.

15.3.9.2 Off-label Paediatric Use (less than 12 years)

Cases with Nuvaxovid:

No ICSR was retrieved for the current reporting interval.

Cumulatively, 12 ICSRs were retrieved (2 males, 4 females, 6 individuals of unspecified sex; age range neonate, infant and 4 – 9 years, when reported). The 12 cumulative ICSRs included 21 AEs of which 1 was serious.

Nine of 12 ICSRs were reported in the infant and child age group (1 infant and 8 children) and included 14 AEs. The most frequently reported AEs (n≥2) were coded to PTs of Product administered to patient of inappropriate age (n=5), No adverse event (n=4) and Vaccination error (n=2).

Three of 12 ICSRs were reported in the neonatal age group and included 7 AEs coded to PTs: Foetal exposure during pregnancy (n=3), Low birth weight baby (n=1), Neonatal respiratory distress (n=1), Premature baby (n=1), and Suspected COVID-19 (n=1).

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (2 males, age [redacted] and [redacted] years and 1 female neonate). The 3 cumulative ICSRs included 4 non-serious AEs.

Two of the 3 ICSRs in were reported in the child age group and included 2 AEs coded to PTs: Wrong product administered (n=1) and Incorrect dose administered (n=1).

One of the 3 ICSRs was reported in the neonatal age group and included 2 AEs coded to PTs: Premature baby (n=1) and Foetal exposure during pregnancy (n=1).

No safety signal was identified.

15.3.10 Tinnitus

The safety topic of Tinnitus was designated as a validated signal on 14-Nov-2022. This signal was confirmed on 18-Jan-2023, and the CCDS was updated to include tinnitus in Section 4.8. Subsequently, in response to US FDA (27-Sep-2023) and EMA (11-Jan-2024) population-based assessments and known limitations of post-authorization data, NVX updated the final disposition of the signal tinnitus to "refuted" as of 01-Apr-2024 and updated the CCDS accordingly. Tinnitus will remain in the post authorization section of the Australian Product Information (Section 4.8). Events of tinnitus continue to be monitored under routine pharmacovigilance.

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for tinnitus (refer to Appendix 14).

Cases with Nuvaxovid:

One initial ICSR was retrieved during the current reporting interval.

Cumulatively, 87 ICSRs were retrieved (30 males, 53 females, 4 individuals of unspecified sex, age range 20 – 75 years, when reported). The 87 cumulative ICSRs included 87 AEs coded to PT Tinnitus. Of the 87 AEs reported, 18 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 12 medically significant (based on medical judgement), 2 hospitalisation and 5 disability.

Cases with Nuvaxovid XBB.1.5:

Five initial and 1 follow-up ICSRs were retrieved during the current reporting interval. The follow-up case included additional information that qualified the ICSR for this interval.

Cumulatively, 9 ICSRs were retrieved (2 males, 6 females, 1 individual of unspecified sex, age range of 30 – 71 years, when reported). The 9 cumulative ICSRs included 9 non-serious AEs coded to PT Tinnitus.

No safety signal was identified.

15.3.11 Vaccine Anxiety-Related Reactions

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for vaccine anxiety related reactions (refer to Appendix 14).

Cases with Nuvaxovid:

Two initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 58 ICSRs were retrieved (7 males, 47 females, 4 of unspecified sex, age range 19 – 75 years, when reported). The 58 cumulative ICSRs included 58 AEs coded to PTs: Anxiety (n=44), Nervousness (n=6), Agitation (n=4), Stress (n=3), and Tension (n=1). Of the 58 AEs reported, 7 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 3 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 3 hospitalisation, and 1 disability.

Cases with Nuvaxovid XBB.1.5:

Two initial and 1 follow-up ICSRs have been retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (1 male, 3 females, age range 32 – 74 years). The 4 cumulative ICSRs included 4 AEs coded to PTs: Anxiety (n=2), Nervousness (n=1) and Stress (n=1). Of the 4 AEs reported, none were serious.

No safety signal was identified.

15.3.12 Vaccination Failures / Lack of Efficacy

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for vaccination failures/lack of efficacy (refer to Appendix 14).

NVX defines vaccination failure as meeting the below 3 criteria, as recommended in "Detailed Guidance on ICSRs in the context of Covid-19" provided by the European Medicines Agency (07-Apr-2022):

1. Associated Covid-19 symptoms are reported.

2. The reported events occur after the normal time period for the protection to be acquired as a result of immunisation in line with the suspected vaccine product information. This time period is defined by NVX to be occurring 7 or more days past the date of the second vaccination, or booster administration.

3. A positive diagnostic test for Covid-19 is also reported in the case.

15.3.12.1 Results and Discussion

Cases with Nuvaxovid:

Four initial and 1 follow-up ICSRs were retrieved for the current reporting interval. The follow-up case included an additional PT that qualified the ICSR for this interval.

Cumulatively, 22 ICSRs were retrieved (7 males, 14 females and 1 individual of unspecified sex, age range 20 – 75 years, when reported). The 22 cumulative ICSRs included 22 AEs coded to PTs: Vaccination failure (n=17), Drug ineffective (n=4), and Paradoxical drug reaction (n=1). Of the 22 AEs reported, 20 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 19 medically significant (based on medical judgement), 1 hospitalisation, and 1 disability.

Cases with Nuvaxovid XBB.1.5:

Three initial and 1 follow-up ICSRs were retrieved for the current reporting interval. The follow-up case included an additional PT that qualified the ICSR for this interval.

Cumulatively, 6 ICSRs were retrieved (1 male, 2 females, and 3 individuals of unspecified sex, age range 46-61 years, when reported). The 6 cumulative ICSRs included 6 AEs, all coded to PT of Vaccination failure. All 6 AEs was serious due to medically significant criteria (based on medical judgement).

15.3.12.2 Conclusion

No safety signal was identified.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of Safety Concerns

A summary of important safety concerns at the beginning of the reporting interval is provided in Table 28, obtained from the EU Risk Management Plan (RMP) v4.2, dated 13-Nov-2023. During the reporting period, the EU RMP was updated to v4.3, dated 06-Mar-2024 to support inclusion of the Nuvaxovid XBB.1.5 variant vaccine and again to v5.1, dated 14-Jun-2024 to support inclusion of the JN.1 variant vaccine. There were no changes to the list of safety concerns during the above-mentioned revisions.

Table 28: Summary of Safety Concerns at the Beginning of the Reporting Interval

Summary of Safety Concerns	
Important identified risk	Myocarditis and/or pericarditis
Important potential risk	Vaccine associated enhanced disease, including vaccine-associated enhanced respiratory disease

Table 28: Summary of Safety Concerns at the Beginning of the Reporting Interval

Summary of Safety Concerns	
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) Use in patients with autoimmune or inflammatory disorders Interaction with other vaccines Long-term safety

16.2 Signal Evaluation

During the reporting interval, two new signals of migraine and tachycardia were validated following health authority requests from TGA and FDA respectively. Both the signals were refuted upon evaluation.

The disposition of the previously validated signal of tinnitus was updated from confirmed to refuted during the reporting interval. Determining the sufficiency of the evidence supporting a causal association between vaccine administration and an adverse event is complex, requires judgement and may evolve over time. In response to US FDA and EMA population-based assessments and known limitations of post-authorisation data, Novavax updated the final disposition of the signal tinnitus to status "refuted". Accordingly, tinnitus was removed from the adverse reactions from post-marketing experience section (Section 4.8) of the CCDS v10.0, effective date: 30-May-2024. Tinnitus will remain in the post authorisation section of the Australian Product Information (Section 4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance.

Summary results of evaluations of validated/non-validated signals evaluated and closed during the reporting interval are presented below.

16.2.1 Migraine

A safety signal was identified by the Australian Therapeutic Good Administration by communication received on 25-Jan-2024 that included a request for the addition of migraine to the Product Information for Nuvaxovid in Section 4.8 Adverse Effects (Undesirable Effects). To further evaluate the TGA request, a comprehensive review of safety data relevant to migraine from clinical trials and the post-authorization safety database was performed, resulting in a refuted status. The Signal Evaluation Report (SER) is included in Appendix 21.

16.2.1.1 Results and Discussion

Across the Integrated Safety Summary, events of migraine were balanced across treatment and placebo groups. No signal was detected quantitatively or qualitatively across the global

post authorization safety data for new onset migraine or disease exacerbation in individuals with medical history of migraine.

16.2.1.2 Conclusion

No evidence of a causal association between Nuvaxovid and migraine beyond temporal association was identified, and the signal was refuted.

16.2.2 Tachycardia

On 21-Mar-2024, FDA Center for Biologics Evaluation and Research requested a reassessment of the signal of tachycardia following review of SSR No.26 (reporting interval 01-Feb-2024 to 29-Feb-2024). In response to this request, a comprehensive review of safety data from clinical trials and the post-authorisation safety database was performed. The SER is included in Appendix 22.

16.2.2.1 Results and Discussion

Across the clinical development Integrated Safety Summary for NVX-CoV2373, in the Pre-crossover and Post-crossover periods, events of tachycardia were infrequent and balanced between active and placebo groups with no meaningful risk differences.

For the post-authorisation data, a total of 224 ICSRs were retrieved by the narrow search strategy, of which 106 met inclusion criteria with a time to onset of 0 – 5 days and which were not clearly attributable, by initial review of co-reported PTs and medical history, to a specific physiologic trigger or diagnosis. Of the 106 reports that met initial inclusion criteria for review, 20 cases were assessed as inconsistent with a causal association based on medical history and/or concurrent events that supported a reasonable alternative etiology. For 34 cases, causal association was assessed as indeterminate.

16.2.2.2 Conclusion

No evidence of a causal association between Nuvaxovid and tachycardia beyond temporal association was identified and the signal was refuted.

16.2.3 Tinnitus

The safety topic of Tinnitus was designated as a validated signal on 14-Nov-2022 following a PRAC preliminary assessment of PBRER No.01 and a subsequent request by the TGA, Australia to update the label. The signal was confirmed upon evaluation and CCDS was updated to add tinnitus to the adverse reactions from post-marketing experience section. Subsequently, label update requests were rejected by both US FDA and EMA citing insufficient evidence to support a causal association with Nuvaxovid.

Determining the sufficiency of the evidence supporting a causal association between vaccine administration and an adverse event is complex, requires judgement and may evolve over time. In response to US FDA and EMA population-based assessments and known limitations of post-authorisation data, Novavax updated the final disposition of the signal tinnitus to status "refuted". Accordingly, tinnitus was removed from the adverse reactions from post-marketing experience section (Section 4.8) of the CCDS v10.0, effective date: 30-May-2024. However, tinnitus will remain in the post authorisation section of the Australian Product Information (Section 4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance including information regarding plausible mechanisms. The SER was presented in Appendix 23.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Identified Risks

16.3.1.1 Myocarditis and/or Pericarditis

On 01-Sep-2022, myocarditis and/or pericarditis was reclassified from an important potential risk to an important identified risk for Nuvaxovid in the core (EU) RMP v2.1. The EU SmPC variation to include myocarditis and/or pericarditis was approved on 25-Oct-2022. Myocarditis and/or pericarditis remains a closely monitored AESI for further characterisation in the post-authorisation setting through routine pharmacovigilance practices, within post-authorisation safety studies and across clinical development programs.

For the analysis in this section, the global vaccine safety database was queried for interval and cumulative ICSRs using the broad search strategy for myocarditis and pericarditis. Of note, this differs from the narrow search strategy utilised in Section 15.2.24 for the O/E analysis.

- Narrow search strategy: Standardised MedDRA Query (SMQ) (Narrow): Non-infectious myocarditis/pericarditis; HLTs: Non-infectious myocarditis; Non-infectious pericarditis.
- Broad search strategy: SMQ (Broad): Non-infectious myocarditis/pericarditis; HLTs: Infectious myocarditis; Infectious pericarditis; Non-infectious myocarditis; Non-infectious pericarditis.

While a specific narrow search strategy is useful for retrieving ICSRs for O/E analysis prior to performing adjudication against a case definition, the broad search strategy allows for the identification of additional potential cases of myocarditis and pericarditis that may not be captured by the narrow search strategy. As the broad search strategy is less specific, all reports retrieved by the broad search strategy were adjudicated against the Brighton Collaboration case definitions for myocarditis and pericarditis. In addition, all reports were reviewed at the case level and in aggregate for evidence of causality, including temporal association with administration of Novavax COVID-19 vaccines and the presence of any alternative etiologies.

Cases with Nuvaxovid:

Five initial and 3 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 136 ICSRs were retrieved (60 males, 76 females, age range 18 – 83 years, when reported). The 130 cumulative ICSRs included 171 AEs, with the most frequently reported PTs (n>5): Pericarditis (n=57), Myocarditis (n=24), Electrocardiogram abnormal (n=13), Extrasystoles (n=11), Myopericarditis (n=7), Troponin increased (n=7), Pericardial effusion (n=6), Ventricular extrasystoles (n=6), and Echocardiogram abnormal (n=5). Of the 171 AEs reported, 137 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 129 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 49 hospitalisation, 5 life-threatening, and 3 deaths. Of these 136 ICSRs, 52 met Level 1 – 3 Brighton Collaboration case definitions for myocarditis and/or pericarditis. Demographics and case characteristics of the cases that met a case definition are summarised in Table 29 and Table 30, respectively.

Cases with Nuvaxovid XBB1.5:

11 initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 15 ICSRs were retrieved (8 males, 6 females, 1 of unknown sex, age range 14 – 91 years, when reported). The 15 cumulative ICSRs included 17 AEs, with the most frequently reported PTs (n≥3): Extrasystoles (n=5), and Pericarditis (n=3). Of the 17 AEs reported, 10 were serious, with the events meeting the following criteria: 9 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 3 hospitalization and 2 death. Of these 15 ICSRs, none met Level 1 -3 Brighton Collaboration case definitions for myocarditis and/or pericarditis.

Data from South Korea, published by the KDCA, reported a total of 5 confirmed cases of myocarditis with Nuvaxovid (adjudicated against a modified algorithm based on the Brighton Collaboration case definition). Four of the 5 confirmed cases have been received as ICSRs in the NVX safety database and are considered as Level 1 – 3 (exact level unknown). No cases were reported with Nuvaxovid XBB.1.5.

Table 29: Demographics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Sex/Age	Nuvaxovid (n=52)		Nuvaxovid XBB.1.5 (n=0)	
	Number of Reports	Percentage of Total (%)	Number of Reports	Percentage of Total (%)
Male	**22**	**42.3**	**0**	**0**
18 – 29	6	11.5	0	0
30 – 39	7	13.5	0	0
40 – 49	6	11.5	0	0

Table 29: Demographics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Sex/Age	Nuvaxovid (n=52)		Nuvaxovid XBB.1.5 (n=0)	
	Number of Reports	Percentage of Total (%)	Number of Reports	Percentage of Total (%)
50 – 59	2	3.8	0	0
UNK	1	1.9	0	0
Female	**28**	**57.7**	**0**	**0**
18 – 29	4	7.7	0	0
30 – 39	8	15.4	0	0
40 – 49	5	9.6	0	0
50 – 59	8	15.4	0	0
60+	5	9.6	0	0

Table 30: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)		Nuvaxovid XBB.1.5 (n=0)	
		Number of Reports	Percentage of Reports (%)	Number of Reports	Percentage of Reports (%)
Number of Reports		52	100.0	0	0
Country of Incidence	Australia	30	57.7	0	0
	Germany	6	11.5	0	0
	Korea, Republic of	5	9.6	0	0
	Italy	3	5.8	0	0
	France	3	5.8	0	0
	Austria	2	3.8	0	0
	Finland	1	1.9	0	0
	Greece	1	1.9	0	0
	United States	1	1.9	0	0
Seriousness Criteria [a]	Medically Significant	39	75.0	0	0
	Hospitalisation	13	25.0	0	0
	Life-threatening	1	1.9	0	0

Table 30: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)		Nuvaxovid XBB.1.5 (n=0)	
		Number of Reports	Percentage of Reports (%)	Number of Reports	Percentage of Reports (%)
Co-reported PTs (n ≥ 5)	Chest pain	27	51.9	0	0
	Pericarditis	18	34.6	0	0
	Dyspnoea	15	28.8	0	0
	Palpitations	10	19.2	0	0
	Myocarditis	10	19.2	0	0
	Headache	10	19.2	0	0
	Dizziness	9	17.3	0	0
	Fatigue	8	15.4	0	0
	Electrocardiogram abnormal	8	15.4	0	0
	Chest discomfort	7	13.5	0	0
	Myalgia	6	11.5	0	0
	Tachycardia	5	9.6	0	0
	Paraesthesia	5	9.6		
	Arthralgia	5	9.6		
	Nausea	5	9.6		
Recurrent Myocarditis/Pericarditis [b]		7	13.5	0	0
Brighton Collaboration Level [c]	Level 1	5	9.6	0	0
	Level 2	34	65.4	0	0
	Level 3	9	17.3	0	0
	Level 1 – 3 (exact level unknown) [e]	4	7.7	0	0

Table 30: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)		Nuvaxovid XBB.1.5 (n=0)	
		Number of Reports	Percentage of Reports (%)	Number of Reports	Percentage of Reports (%)
Time to Onset (Days) [d]	0 – 7	26	50.0	0	0
	8-14	9	17.3	0	0
	> 15	7	13.5	0	0
	UNK	10	19.2	0	0
Outcome [f]	Not Recovered/Not Resolved	22	42.3	0	0
	Unknown	22	42.3	0	0
	Recovering/Resolving	9	17.3	0	0
	Recovered/Resolved	5	9.6	0	0
	Recovered with Sequelae	2	3.8	0	0

[a] Reflects event level seriousness of PTs that were retrieved by the search strategy.

[b] Classification of recurrent myocarditis/pericarditis refers to reports where the prior myocarditis/pericarditis or reported chest pain was experienced after vaccination with a non-company product, viral infection, or due to an unknown cause.

[c] If a case met a different level of certainty for myocarditis and pericarditis, then the highest level was chosen for representation in this section.

[d] Time to onset was assessed based on review of case narratives and onset of first symptoms, which may have preceded formal diagnosis. If no onset date was available, then the date of Health Authority receipt of the report was used as the date of onset. Therefore, the event latency listed in this table may differ from latency listed in other outputs attached to this report.

[e] Adjudication is based on assessment by KDCA against modified Brighton Collaboration.

[f] The outcome for PTs retrieved by the search strategy is summarized in this section.

No significant safety information was received on this important identified risk of myocarditis and/or pericarditis during the reporting interval that would alter its already established characterisation.

16.3.2 New Information on Important Potential Risks

16.3.2.1 Vaccine-Associated Enhanced Disease, Including Vaccine-Associated Enhanced Respiratory Disease

This topic of vaccine-associated enhanced disease or vaccine-associated enhanced respiratory disease is also monitored as an AESI and further information can be found in Section 15.2.39.

16.3.3 New Information on Other Potential Risks Not Categorised as Important:

Not applicable.

16.3.4 New Information on Other Identified Risks Not Categorised as Important:

Cumulatively, anaphylaxis is an identified risk for Nuvaxovid that is not categorised as important. A detailed analysis of this topic is presented in Section 15.2.2. This topic will continue to be monitored via routine pharmacovigilance activities.

16.3.5 Update on Missing Information

16.3.5.1 Update on Missing Information: Use in Pregnancy and While Breastfeeding

There is limited experience with use of Nuvaxovid in pregnant women. It is unknown whether Nuvaxovid is secreted in human milk.

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in pregnancy and while breastfeeding (refer to Appendix 14).

16.3.5.1.1 Use in Pregnancy

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in pregnancy (refer to Appendix 14).

16.3.5.1.1.1 Results and Discussion

<u>Cases with Nuvaxovid:</u>

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 14 ICSRs were retrieved (14 females, age range 19 – 57 years) with 41 AEs. The 14 ICSRs had 18 pregnancy related PTs: Maternal exposure during pregnancy (n=7), Abortion spontaneous (n=4), Exposure during pregnancy (n=2), and Pre-eclampsia (n=2), Gestational hypertension (n=1), Placental infarction (n=1), Premature delivery (n=1). Of the pregnancy related AEs retrieved, 6 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 6 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

Three initial and 6 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 16 ICSRs were retrieved (16 females, age range 26 – 42 years). The 16 cumulative ICSRs included 20 pregnancy associated AEs coded to PTs: Maternal exposure during pregnancy (n=13), Exposure during pregnancy (n=3), Polymorphic eruption of pregnancy (n=1), Premature delivery (n=1), Abortion spontaneous (n=1), and Gestational hypertension (n=1). Of the 20 pregnancy associated AEs retrieved, 1 AE was serious, meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria).

An analysis could not be performed as gestational age, obstetric details, medical history, concomitant medication, and further details were unknown. None of the reports of use in pregnancy raises any safety concerns.

16.3.5.1.1.2 Conclusion

No safety signal was identified.

16.3.5.1.2 Foetal and neonate ICSRs (Exposure during Pregnancy)

The global vaccine safety database was queried for the cumulative period up to 19-Jun-2024 for the patient age group of foetus and neonate and are manually reviewed to confirm exposure during pregnancy.

16.3.5.1.2.1 Results and Discussion

Cases with Novavax COVID-19 Vaccine, Adjuvanted:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (1 male, 2 females, 1 individual of unspecified sex; age group:1 foetus and 3 neonates). The 3 neonates were exposed to Novavax COVID-19 vaccine, adjuvanted via transplacental route. The 4 cumulative ICSRs included 16 AEs coded to PTs Foetal exposure during pregnancy (n=3), and n=1 for each of the following PTs: COVID-19, Bronchiolitis, Milk allergy, Immune system disorder, Reflux laryngitis, Infantile apnoea, Choking, Large for dates baby, Maternal exposure during pregnancy, Suspected COVID-19,

Neonatal respiratory distress, Low birth weight baby and Premature baby. Of the 16 total AEs reported, 10 were serious, with all the events meeting the following criteria: medically significant (based on medical judgement or serious by convention, meeting IME criteria) and hospitalization.

Cases with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula):

One initial and 1 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (1 male foetus, 1 individual of unspecified sex foetus and 1 female neonate). The neonate was exposed to Novavax COVID-19 vaccine Adjuvanted (2023-2024 Formula) via transplacental route. The 3 cumulative ICSRs included 6 AEs coded to PTs: Foetal exposure during pregnancy (n=3), Foetal heart rate deceleration abnormality (n=1), Large for dates baby (n=1) and premature baby (n=1). Of the 6 AEs reported, 1 AE was serious with the event meeting the medically significant seriousness criterion (based on medical judgement or serious by convention, meeting IME criteria).

16.3.5.1.2.2 Conclusion

No safety signal was identified.

16.3.5.1.3 Use while breastfeeding

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use while breastfeeding (refer to Appendix 14).

16.3.5.1.3.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (3 females, age range 29 – 38 years). The 3 cumulative ICSRs included 3 AEs coded to PTs: Exposure via breast milk (n=1), Lactation insufficiency (n=1), and Lactation puerperal increased (n=1). Of the 3 AEs reported, none were serious. These non-serious reports of use during breastfeeding do not raise any safety concerns.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

None of the reports of use during pregnancy and breastfeeding raised any safety concerns.

16.3.5.1.3.2 Conclusion

No safety signal was identified.

16.3.5.2 Update on Missing Information: Use in Immunocompromised Patients

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in immunocompromised patients (refer to Appendix 14). An increase in ICSRs, above what is expected by typical patterns of reporting, was retrieved for this search relative to the prior PBRER. No notable differences or trends have been detected across the general and immunocompromised populations on review of new ICSR inclusions to the dataset.

16.3.5.2.1 Results and Discussion

Cases with Nuvaxovid:

Six initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 29 ICSRs were retrieved (5 males, 21 females, 3 of unspecified sex, age range 35 – 93 years). The 29 cumulative ICSRs included 102 AEs. The most frequently reported AEs (n>1) included: Off label use (n=7), COVID-19 immunisation (n=7), Dyspnoea (n=4), Fatigue (n=3), Pyrexia (n=3), Palpitations (n=2), Taste disorder (n=2), Syncope (n=2), Chest pain (n=2), Pain in extremity (n=2), Cough (n=2), Guillain-Barre syndrome (n=2), and Rash (n=2). Of the 102 AEs reported, 32 were serious with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 28 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 13 hospitalisation, 7 life threatening, and 3 disability.

Cases with Nuvaxovid XBB.1.5:

Four initial and 2 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 6 ICSRs was retrieved (3 females, 3 of unspecified sex, age 63 years, when reported). The 6 cumulative ICSRs included 24 AEs. The most frequently reported AEs (n>1) included: Asthenia (n=2), COVID-19 (n=2), Pain in extremity (n=2), and Sinus congestion (n=2). Of the 24 AEs reported, 4 were serious with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 2 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 2 hospitalisation, and 1 death.

16.3.5.2.2 Conclusion

Review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

No safety signal was identified.

16.3.5.3 Update on Missing Information: Use in Frail Patients with Comorbidities (e.g., Chronic Obstructive Pulmonary Disease [COPD], Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease , diabetes, chronic neurological disease, cardiovascular disorders) (refer to Appendix 14).

16.3.5.3.1 Results and Discussion

Cases with Nuvaxovid:

Twenty-five initial and 18 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 645 ICSRs were retrieved (168 males, 449 females, 28 individuals of unspecified sex, age range 13 – 96 years, when reported). The 645 cumulative ICSRs included 2835 AEs. The most frequently reported PTs (n>50) were Headache (n=122), Fatigue (n=114), Myalgia (n=71), Pyrexia (n=68), Dizziness (n=59), and Chest pain (n=55), Injection site pain (n=54), Pain in extremity (n=53), and Nausea (n=53). Of the 2835 AEs reported, 737 were serious (including 21 fatal AEs). No safety signal was identified.

Cases with Nuvaxovid XBB.1.5:

76 initial and 14 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 131 ICSRs were retrieved (34 males, 78 females, 19 individuals of unspecified sex, age range 14 – 94 years, when reported). The 131 cumulative ICSRs included 536 AEs. The most frequently reported PTs (n≥10) were Pain in extremity (n=22), Fatigue (n=17), Pyrexia (n=15), Headache (n=15), Maternal exposure during pregnancy (n=13), COVID-19 (n=12), Unevaluable event (n=12), Pain (n=11), Nausea (n=10), and Dizziness (n=10). Of the 536 AEs reported, 74 were serious (including 20 fatal AEs). No safety signal was identified.

16.3.5.3.2 Conclusion

Review of individual reports did not suggest any trends for the adverse event profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

No safety signal was identified.

16.3.5.4 Update on Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

There is limited information on the safety of Nuvaxovid in patients with autoimmune or inflammatory disorders. There is no evidence from clinical studies to date that the safety profile of this population differs from that of the general population.

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in patients with autoimmune or inflammatory disorders (refer to Appendix 14).

16.3.5.4.1 Results and Discussion

Cases with Nuvaxovid:

Eleven initial and 6 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 211 ICSRs were retrieved (35 males, 172 females and 4 individuals of unknown sex, age range 21 – 94 years, when reported). The 211 cumulative ICSRs included 992 AEs. The most frequently reported AEs (n≥20) were Headache (n=45), Fatigue (n=35), Pyrexia (n=29), Myalgia (n=26), Pain in extremity (n=22), Dizziness (n=21), Nausea (n=20). Of the 992 AEs reported, 263 were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 203 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 86 hospitalisation, 14 life-threatening, 44 disability, and 18 death.

Cases with Nuvaxovid XBB.1.5:

Thirty-one initial and 3 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 54 ICSRs were retrieved (14 males, 32 females and 8 individuals of unknown sex, age range 29 – 84 years, when reported). The 54 cumulative ICSRs included 230 AEs. The most frequently reported AEs were (n≥5) Pain in extremity (n=10), Fatigue (n=8), Pyrexia (n=7), COVID-19 (n=7), Headache (n=7), Dizziness (n=6), Nausea (n=6), Malaise (n=6), and Unevaluable event (n=5). Of the 230 AEs reported, 31 were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 12 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 9 hospitalisation, 1 life-threatening, 7 disability, and 13 death.

16.3.5.4.2 Conclusion

Review of individual reports did not suggest any trends for the adverse event profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

No safety signal was identified.

16.3.5.5 Update on Missing Information: Interaction with Other Vaccines

There is limited information on the safety of Nuvaxovid when administered with other vaccines, except for seasonal influenza vaccine.

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for reports of interaction with other vaccines (refer to Appendix 14).

All the reports retrieved based on the search strategy were further filtered manually for vaccines from the non-company co-suspect field and concomitant drugs field for further review and assessment.

16.3.5.5.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, ages 41 and 46 years). The reports retrieved were manually reviewed for any vaccines listed in the non-company co-suspect field or concomitant drugs field. After assessment, it was identified that both reports did not meet the inclusion criteria.

Cases with Nuvaxovid XBB.1.5:

No ICSRs have been retrieved either cumulatively or for the current reporting interval.

16.3.5.5.2 Conclusion

During the reporting interval and cumulatively, no new information determining interaction with other vaccines was identified.

No safety signal was identified.

16.3.5.6 Update on Missing Information: Long-Term Safety

Long-term safety is monitored by evaluation of the post-authorisation data over time. Understanding of the long-term safety profile of Nuvaxovid is currently limited.

16.3.5.6.1 Results and Discussion

Long-term safety is evaluated by routine monitoring of post-authorisation safety studies. There were 3 ongoing post-authorisation safety studies during the reporting interval and no clinically significant safety findings were reported from any of those studies, as summarised in Appendix 9 Table 39.

16.3.5.6.2 Conclusion

During the reporting interval and cumulatively, no new information determining long-term safety was identified.

16.4 Characterisation of Risks

Risk characterisation for important identified risks, important potential risks and missing information are discussed in EU RMP Part II, module SVII, based on the latest version of EU RMP, v5.1, dated 14-Jun-2024.

16.5 Effectiveness of Risk Minimisation

Not applicable. There are no additional risk minimisation measures in place for Nuvaxovid or Nuvaxovid XBB.1.5. Routine risk minimisation activities are considered to be sufficient for monitoring all important identified risks, important potential risks and missing information.

17 BENEFIT EVALUATION

This section provides a baseline and newly identified benefit information for Novavax's two COVID-19 vaccines currently authorized in the EU - Nuvaxovid and Nuvaxovid XBB.1.5 – which in turn supports the benefit-risk characterisation in Section 18. This section also provides baseline and newly identified benefit information for 3 Novavax study vaccines (NVX-CoV2373, NVX-CoV2515, NVX-CoV2540).

17.1 Important Baseline Efficacy and Effectiveness Information

This section provides baseline benefit information for Nuvaxovid and Nuvaxovid XBB.1.5 at the start of the reporting interval of this PBRER (20-Dec-2023) for Nuvaxovid and Nuvaxovid XBB.1.5.

The baseline benefit information is the efficacy/effectiveness and immunogenicity data in v9.0 (dated 19-Dec-2023) of the Novavax COVID-19 Vaccine (recombinant, adjuvanted) Global CCDS in effect at the start of the PBRER reporting interval on 20-Dec-2023.

Baseline clinical efficacy and immunogenicity of Nuvaxovid were evaluated in two pivotal, placebo-controlled, Phase 3 clinical trials: ongoing Study 2019nCoV-301 conducted in North America and completed Study 2019nCoV-302 conducted in the UK.

Baseline effectiveness of Nuvaxovid XBB.1.5 for individuals 12 years of age and older was inferred from studies which evaluated the primary series and booster vaccination with Novavax COVID-19 Vaccine (recombinant, adjuvanted) Original, Wuhan strain and supported by studies of booster doses of two study vaccines that targeted two other Omicron variants, the Omicron BA.1 (NVX-CoV2515) and Omicron BA.5 (NVX-CoV2540) variants, in completed Study 2019nCoV-311.

17.1.1 Adolescents 12 to <18 years of age

17.1.1.1 Primary Series (Original, Wuhan strain)

17.1.1.1.1 Efficacy in Adolescents 12 to <18 years of age

Efficacy and immunogenicity of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adolescent participants 12 to <18 years of age were assessed in the ongoing paediatric expansion portion of Study 2019nCoV-301 (US).

A total of 1,799 participants assigned in a 2:1 ratio to receive two doses of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=1,205) or placebo (n=594) by intramuscular injection 21 days apart represented the primary efficacy population.

COVID-19 was defined as the first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least one or more of the pre-defined symptoms within each severity

category. There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (Novavax COVID-19 Vaccine (recombinant, adjuvanted), n=6; placebo, n=14) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8%, 92.1%).

At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern (VOC) was the predominant variant circulating in the US and accounted for all cases where sequence data were available (11/20, 55%).

17.1.1.1.2 Immunogenicity in Adolescents 12 to <18 years of age

An analysis of the SARS-CoV-2 neutralizing antibody response 35 days after Dose 2 was conducted in adolescent participants seronegative to anti-SARS-CoV-2 nucleoprotein /PCR-negative at baseline compared with that observed in seronegative/PCR-negative adult participants aged 18 to less than 26 years from the adult main study (Per Protocol Immunogenicity (PPIMM) Population, before crossover). Noninferiority (lower bound 95% CI for the geometric mean ratio [GMR] >0.67 [1.25]) was met.

17.1.1.2 Booster dose (Original, Wuhan strain)

17.1.1.2.1 Immunogenicity in Adolescents 12 to <18 years of age

The safety and immunogenicity of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was evaluated in the ongoing paediatric expansion portion of Study 2019nCoV-301, involving 220 adolescents 12 to <18 years of age conducted in the US. Of these, 110 participants received a booster dose after first receiving placebo during the initial (pre-crossover) vaccination period followed by active vaccination during the blinded crossover period [Cohort 1] and 110 who received a booster dose after first receiving active vaccination during the initial (pre-crossover) vaccination period followed by placebo during the blinded crossover period [Cohort 2]) from 58 sites in the US. All adolescent participants aged 12 to < 18 years were seronegative to SARS-CoV-2 at baseline.

This study assessed the immune response as neutralizing antibody against SARS-CoV-2 wild-type virus, serum IgG antibody to SARS-CoV-2 S protein immediately prior to and at 28 days after administration of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) and evaluated the overall safety profile of Novavax COVID-19 Vaccine (recombinant, adjuvanted) through 28 days after the booster dose in 220 randomly selected adolescent participants aged 12 through <18 years.

A total of 2,122 participants received two doses of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A total of 1,499 participants received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) approximately 9 months after completing the primary vaccination series, and of those 220 were selected for immunogenicity analysis. This resulted in 53 participants eligible to be analysed as part of the primary endpoint.

A single booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) induced an approximate 34.2-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose with a serum IgG geometric mean ELISA unit (GMEU) of 388,263.3 EU/mL compared to a GMEU of 11,339.4 EU/mL pre-booster and an approximate 2.5-fold increase from peak GMEU (156,286.4 EU/mL), 14 days following Dose 2 of the primary series.

An approximate 27.7-fold increase in neutralizing antibodies was shown from a GMT of 426.7 pre-booster to a GMT of 11824.4 post-booster and an approximate 2.7-fold increase from a peak GMT (14 days post-Dose 2) of 4434.0.

A single booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) administered to adolescent participants 12 to <18 years of age elicited robust immune responses (neutralizing antibody (MN_{50}), serum IgG antibody, and hACE2 receptor binding inhibition) against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) and were higher than those reported at 14 days after the second dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) of the primary vaccination series. Based on neutralizing antibody responses, non-inferiority was achieved for GMFRs and for the differences in seroconversion rates using the baseline of the first dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in the pre-crossover period (Cohort 2). Higher immune responses for pseudovirus-based neutralizing antibody against the Omicron BA.4/5 variant and serum IgG antibody against the Omicron BA.1 variant were also seen after the single booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted).

17.1.2 Adults 18 years of age and older

17.1.2.1 Primary Series - Original, Wuhan strain

17.1.2.1.1 Efficacy in Adults 18 years of age and older

Upon enrollment in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive Novavax COVID-19 Vaccine (recombinant, adjuvanted) or placebo.

17.1.2.1.1.1 Study 2019nCoV-301 - Original, Wuhan strain

Study 2019nCoV-301 is an ongoing 4-part Phase 3, multicentre, randomized, observer-blinded, placebo-controlled study with an adult main study conducted in participants 18 years of age and older in the US and Mexico and a paediatric expansion occurring in participants 12 < 18 years of age in the US. Upon enrollment in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive Novavax COVID-19 Vaccine (recombinant, adjuvanted) or placebo.

The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=17,312) or placebo (n=8,140), received two doses (Dose 1 on day 0; Dose 2 at day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received Novavax COVID-19 Vaccine (recombinant, adjuvanted) and those who received placebo.

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19. There were no meaningful differences in overall vaccine efficacy in participants who were at increased risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g., body mass index $\geq$ 30 kg/m^2, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrollment that occurred during the time period when strains classified as VOCs or Variants of Interest (VOIs) were predominantly circulating in the 2 countries (US and Mexico) where the study was conducted.

Vaccine efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) to prevent the onset of COVID-19 from seven days after Dose 2 was 90.4% (95% CI 82.9 – 94.6). No cases of severe COVID-19 were reported in the 17,312 Novavax COVID-19 Vaccine (recombinant, adjuvanted) participants compared with 4 cases of severe COVID-19 reported in the 8,140 placebo recipients in the PP-EFF analysis set.

Study 2019nCoV-302 - Original, Wuhan strain

2019nCoV-302 is a completed Phase 3, multicentre, randomized, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the UK. Upon enrollment, participants were stratified by age (18 to 64 years and 65 to 84 years) to receive Novavax COVID-19 Vaccine (recombinant, adjuvanted) or placebo.

The primary efficacy analysis set (PP-EFF) included 14,039 participants who received either Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=7,020) or placebo (n=7,019), received two doses (Dose 1 on day 0, Dose 2 at median 21 days) did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received Novavax COVID-19 Vaccine (recombinant, adjuvanted) and participants who received placebo.

Vaccine efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) to prevent the onset of COVID-19 from seven days after Dose 2 was 89.7% (95% CI 80.2 – 94.6). No cases of severe COVID-19 were reported in the 14,039 Novavax COVID-19 Vaccine (recombinant, adjuvanted) participants compared with 5 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.

These results reflect enrollment that occurred during the time period when the B.1.17 (Alpha) variant was circulating in the United Kingdom. Identification of the Alpha variant was based on S gene target failure by PCR.

No cases of severe COVID-19 were reported in the 7,020 Novavax COVID-19 Vaccine (recombinant, adjuvanted) participants compared with 4 cases of severe COVID-19 reported in the 7,019 placebo recipients in the PP-EFF analysis set.

17.1.2.2 Booster Dose - Original, Wuhan strain and Omicron BA.1 and BA.5 variants

17.1.2.2.1 Immunogenicity in Adults 18 years of age and older

17.1.2.2.1.1 Study 2019nCoV-101 Part 2 - Original, Wuhan strain

The safety and immunogenicity of a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was evaluated in the completed Phase 2 randomized, observer-blinded, placebo-controlled clinical study administered as a single booster dose (Study 2019nCoV-101, Part 2) in healthy adult participants aged 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline. Upon enrollment, participants were stratified by age (18 to 64 years; 65 to 84 years) to receive Novavax COVID-19 Vaccine (recombinant, adjuvanted) or placebo.

A total of 255 participants received two doses of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (0.5 mL, 5 micrograms 3 weeks apart) as the primary vaccination series. A subset of 105 participants received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) approximately 6 months after receiving Dose 2 of the primary series.

A single booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) induced a 31.2-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose (Day 217) with serum IgG geometric mean titre (GMT) of 200,243 EU compared to a GMT of 6,151 EU pre-booster (Day 189). A GMR of 4.7 from peak GMT (42,173 EU), 14 days following Dose 2 of the primary series was demonstrated.

A 79.6-fold increase in neutralizing antibodies was shown from a GMT of 68 pre-booster (Day 189) to a GMT of 5,542 post-booster (Day 217). A GMR of 4.0 from a peak GMT (14 days post-Dose 2) of 1,5461 was demonstrated.

17.1.2.2.1.2 Study 2019nCoV-301 - Original, Wuhan strain

In the open-label booster phase of ongoing Study 2019nCoV-301, participants 18 years of age and older received a single booster dose of the Novavax COVID-19 Vaccine (recombinant, adjuvanted) at least 6 months after completion of the primary series. A subset of 226 participants were included in the per-protocol immunogenicity (PP-IMM) analysis set as they did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose.

Pre-specified immunogenicity non-inferiority analyses included an assessment of MN_{50} GMT ratio and difference in seroconversion rates. Seroconversion for a participant was defined as achieving a 4-fold rise in MN_{50} from baseline (before the booster dose and before the first dose of the primary series).

The analysis of the GMT ratio of MN50 following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > 0.67) and point estimate >0.83.

The analysis of the difference in seroconversion rates following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > -10%).

In addition, a single booster dose of the Novavax COVID-19 Vaccine, (recombinant, adjuvanted) elicited a robust immune response (serum IgG antibody) against the Omicron BA.1 variant at 28 days after booster vaccination that were higher than that reported at 14 days after primary series vaccination in the same participants.

Additionally, in Study 301, approximately 6 months after completion of the third dose (first booster) with Novavax COVID-19 Vaccine (recombinant, adjuvanted), 356 participants at selected sites received a fourth dose (second booster) of Novavax COVID-19 Vaccine (recombinant, adjuvanted). Dosing was initiated on 19-Sep-2022, with enrollment completed on 01-Oct-2022. Immunogenicity data were collected from 331 participants immediately prior to administering the fourth dose and at 28 days after vaccination based on data cut-off date of 08-Nov-2022. Safety data were assessed in 356 participants from the time of administration of the second booster dose through the data cut-off date of 08-Nov-2022.

17.1.2.2.1.3 Study 2019nCoV-311 Parts 1 and 2, Original, Wuhan strain and Omicron BA.1 or BA.5 variant

Study 2019nCoV-311 is a completed 2-part, Phase 3, randomized, observer-blinded study conducted in Australia to evaluate the safety and immunogenicity in adults of a booster dose of either the original monovalent Nuvaxovid (NVX-CoV2373), the monovalent study vaccine Omicron BA.1 (NVX-CoV2515), the monovalent study vaccine Omicron BA.5 (NVX-CoV2540), or a bivalent study vaccine (+NVX-CoV2515 or + NVX-CoV2540).

In Part 1, a subgroup of participants 18 to 64 years of age who previously received 3 doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or monovalent vaccine (Omicron BA.1). The booster doses were administered at a median of 182 and 177 days after the last vaccination, respectively. Neutralizing antibody titres for the Omicron BA.1 virus, measured by a microneutralization assay [MN50], were evaluated at 14 days after vaccination. Participants included in the day 14 per protocol analysis set population (n=240) had no serologic or virologic evidence of SARS-CoV-2 infection prior to the booster dose.

Pre-specified immunogenicity analyses included an assessment of MN_{50} GMT ratio and difference in SRRs. SRR was defined as the percentage of participants achieving a 4-fold rise in MN_{50} from baseline (before the first dose of the study vaccine).

The analysis of the GMT ratio following the booster dose with monovalent vaccine (Omicron BA.1) compared to the booster dose with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) met the superiority criterion for success (lower limit of the 95% CI > 1.0).

The lower limit of the two-sided 95% CI for the difference in SRRs (percentage) was 10.3%, which met the non-inferiority criterion for success (lower limit of 95% CI for the percentage difference of >-5%).

In sensitivity analyses using a per protocol analysis set that did not exclude participants with serologic evidence of SARS-CoV-2 infection (PP2 Analysis Subset, n= 491), neutralizing antibody responses against the Omicron BA.1 virus induced by the monovalent vaccine (Omicron BA.1) were compared with neutralizing antibody responses against the Omicron BA.1 virus induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) 14 days after study vaccination.

The GMTs were 318.2 (95% CI: 269.8, 375.3) in the monovalent vaccine (Omicron BA.1) group (n= 247) and 218.1 (95% CI: 186.0, 255.7) in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group (n= 244), resulting in an estimated GMT ratio of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) of 1.5 (95% CI: 1.36, 1.77).

The SRRs (percentage) were 54.3% in the monovalent vaccine (Omicron BA.1) group and 32.0% in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, resulting in a difference in SRRs (percentage) of 22.3% (95% CIs: 13.6%, 30.6%).

In Part 2, a subgroup of participants 18 years of age and older who previously received at least 3 doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or monovalent vaccine (Omicron BA.5). The booster doses were administered a median of 389 and 328 days after the last vaccination, respectively. Neutralizing antibody titters against a pseudovirus expressing the SARS-CoV-2 Spike protein

from the Omicron BA.5 virus, measured by pseudovirus neutralization assay [ID50], were evaluated at 28 days after vaccination. Participants included in the day 28 per protocol analysis set population (n=462) had no virologic evidence of SARS-CoV-2 infection at time of the booster dose.

Exploratory immunogenicity analyses included an assessment of the ID50 GMT ratio and difference in SRRs. SRR was defined as the percentage of participants achieving a 4-fold rise in ID50 from baseline (before the first dose of the study vaccine).

The GMT ratio following the booster dose with monovalent vaccine (Omicron BA.5) compared with the booster dose with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 2.5 (two-sided 95% confidence interval: 2.10, 2.94).

The difference in SRR (percentage) between the booster dose with monovalent vaccine (Omicron BA.5) and the booster dose with Novavax Vaccine, Adjuvanted (Original monovalent) was 33.2% (two-sided 95% confidence interval: 25.4%, 40.7%).

17.1.2.2.1.4 Study 2019nCoV-501 - Original, Wuhan strain

In the completed Phase 2a/b, multicentre, randomized, observer-blinded, placebo-controlled study, the safety and immunogenicity of a booster dose were evaluated in healthy HIV-negative adult participants 18 to 84 years of age and PLWH 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. People living with HIV were medically stable (free of opportunistic infections), receiving highly active and stable antiretroviral therapy, and having an HIV-1 viral load of < 1000 copies/mL.

A total of 1,804 participants (PP-IMM Analysis Set) received a booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) approximately 6 months after completion of the primary series of Novavax COVID-19 Vaccine (recombinant, adjuvanted) (Day 201).

A 17.1-fold increase was shown in serum IgG GMT assessed at Day 236 (114,679 EU) from the pre-boost GMT at Day 201 (5,950 EU). A GMR of 2.2 was demonstrated from peak GMT (52,023 EU) at Day 35 following completion of the primary series.

A 20.6-fold increase in neutralizing antibodies was shown from a GMT of 146 pre-booster (Day 201) to a GMT of 3,726 post-booster (Day 236). A GMR of 2.7 was demonstrated from a peak GMT (14 days post-Dose 2) of 1,352.

17.1.3 Elderly Population

The efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years) for the primary series.

Participants ≥65 years of age were evaluated for efficacy in the two pivotal Phase 3 clinical trials of prototype NVX-CoV2373.

In the placebo-controlled ongoing Phase 3 Study 2019nCoV-301 conducted in the US and Mexico, 11.8% (n=2,048) of enrolled participants that received the primary series were ≥ 65 years.

In the placebo-controlled completed Phase 3 Study 2019nCoV-302 conducted in the United Kingdom, 27.8% (n=1,953) of enrolled participants who received the primary series were ≥ 65 years.

17.2 Newly identified information on efficacy and effectiveness

This section provides new information from the literature available at the end of the reporting interval of this PBRER (19-Jun-2024) on the efficacy/effectiveness or efficacy/effectiveness and immunogenicity of Nuvaxovid, Nuvaxovid XBB.1.5 and NVX study vaccines from the literature (8 publications).

17.2.1 Newly Identified Information on Efficacy and Effectiveness from the Literature (n=2)

"Durability of Protection Against COVID-19 Through the Delta Surge for the NVX-COV2373 Vaccine" reported the results of Novavax's ongoing Study 2019nCoV-301 in characterizing the vaccine's durability of protection. The authors used statistical methods that integrated surveillance data of circulating strains with post-crossover cases, to estimate placebo-controlled vaccine efficacy and durability of NVX-CoV2373 against both pre-Delta and Delta strains of SARS-CoV-2 during Novavax's PREVENT-19 RCT initiated in Apr-2021. The authors reported Vaccine efficacy against pre-Delta strains of COVID-19 was 89% (95% CI: 75%, 95%) and 87% (72%, 94%) at 0 and 90 days after 2 doses of NVX-CoV2373, respectively, with no evidence of waning (p=0.93). Vaccine efficacy against the Delta strain was 88% (71%, 95%), 82% (56%, 92%), and 77% (44%, 90%) at 40, 120, and 180 days, respectively, with evidence of waning (p<0.01). In sensitivity analyses, the estimated Delta vaccine efficacy at 120 days ranged from 66% (15%, 86%) to 89% (74%, 95%) per various assumptions of the surveillance data. The authors results showed that NVX-CoV2373 had high initial efficacy against pre-Delta and Delta strains of COVID-19 with little evidence of waning for pre-Delta strains through 90 days and moderate waning against Delta strains over 180 days. [Follmann 2024]

"*Risk of SARS-CoV-2 breakthrough infection following NVX-CoV2373 and BNT162b2 vaccinations in Korean Adults: A population-based observational study*" reported results from the authors' observational study to evaluate the effectiveness of NVX-CoV2373 and BNT162b2 vaccines in Korean population (≥18 years) following vaccination with either NVX-CoV2373 (n=47,078) or BNT162b2 (n=7,561), with individual-level case data on laboratory-confirmed SARS-CoV-2 infection and vaccination records. Thirty days post-second doses, COVID-19 rates were 7.9% (595 of 7,561) of NVX-CoV2373 recipients and 8.6 % (647 of 7,561) of BNT162b2 recipients. NVX-CoV2373 rates increased to 9.8 % and 11.2 % at 60- and 90-days post-vaccination, while BNT162b2 rates were 10.5 % and 11.3 %

for the same intervals. The 22-week risk ratio for recipients of the NVX-CoV2373 vaccine, compared to recipients of the BNT162b2 vaccine, was 1.11 (95 % CI, 0.99 to 1.25) for laboratory-confirmed SARS-CoV-2 infection. Continued monitoring is essential to evaluate the duration of protection across different vaccine platforms and vaccination schedules. [Kim 2024]

17.2.2 Newly Identified Information on Immunogenicity from the Literature (n=7)

"Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Subvariant Neutralization Following a Primary Vaccine Series of NVX-CoV2373 and BNT162b2 Monovalent Booster Vaccine" presented results from a prospective observational study of the 2-dose primary series of NVX-CoV2373 administered 3 weeks apart, followed by heterologous booster vaccination with BNT162b2 vaccine administered to 30 adults (≥18 years) who continued in the safety follow-up after Novavax Study 2019nCoV-301 ended. The median duration from the second NVX-CoV2373 dose to the BNT162b2 dose was 291 days (interquartile range, 216–315 days). This regimen was immunogenic. Of the 7 participants identified as having had SARS-CoV-2 infection, the diagnosis was made at enrollment for 2 participants and during follow-up for the other 5 participants. At day 29 post-booster, the geometric mean value of the receptor-binding domain (RBD)–specific memory B cell (RBD+MBC) response was 33,908 in SARS-CoV-2–naive participants following the NVX-CoV2373 - BNT162b2 regimen, compared to 20,024 in persons who received 3 doses of mRNA vaccine (P =0.44). At 6 months post-booster, the geometric mean value was 11,715 for the NVX-CoV2373 - BNT162b2 regimen compared to 7,221 following 2 doses of doses of mRNA vaccine. Anti–wild-type spike IgG GMT was boosted approximately 84-fold from day 0 to day 15, followed by a 1.2-fold decrease in GMT from day 15 to month 6 after the booster vaccine. This study demonstrated that priming with 2 doses of NVX-CoV2373 and boosting with BNT162b2 elicited a humoral and cell-mediated immune response to the D614G variant as well as a substantial immune response against some Omicron subvariants. The limitations of this study include the small cohort size, the lack of an mRNA vaccine comparator arm and the lack of testing for epitope-specific responses. [Babu 2024]

"*Immunogenicity of third dose COVID-19 vaccine strategies in patients who are immunocompromised with suboptimal immunity following two doses (OCTAVE-DUO): an open-label, multicentre, randomised, controlled, phase 3 trial*" reported results from OCTAVE-DUO, a prospective, open-label, multicentre, randomised, controlled, phase 3 trial in the UK, investigating humoral and T-cell responses in immunocompromised adults (>18 years) with previous sub-optimal responses to two previous doses of a SARS-CoV-2 vaccine. The primary outcome was vaccine-specific immunity defined by anti-SARS-CoV-2 spike antibodies and T-cell responses to SARS-CoV-2 spike peptides 21 days after the booster (third) vaccine dose compared to pre-third vaccine responses. This 3-arm trial followed patients' humoral and T-cell responses to 1 of 3 types of booster COVID-19 vaccines: BNT162b2 or mRNA-1273 administered to patients in several disease cohorts or NVX-CoV2373 administered only to patients with lymphoid malignancies (n=53, 75% males, 68%≥65 years). In the lymphoid malignancies group, booster vaccination with NVX-

CoV2373 did not appear to be as effective at inducing a serological response as the mRNA-based vaccines, although T-cell responses generated were similar. One serious adverse reaction of diarrhoea occurred in a participant in the NVX-CoV2373 group. The following AEs were experienced by participants in the NVX-CoV2373 arm: vaccination (n=13); headache (n=11); myalgia (n=9); arthralgia (n=5); nausea (n=5); chills (n=4); dyspnoea (n=3); fever/pyrexia (n=3); arrhythmia (n=1). The majority of participants benefited from the additional vaccine, both in terms of serological and T-cell responses affording protection from COVID-19. [Goodyear 2024]

"*Altered IgG4 Antibody Response to Repeated mRNA versus Recombinant Protein SARS-CoV-2 Vaccines*", reported results from Novavax's ongoing Study 2019nCoV-301 and completed Study 2019nCoV-307 of IgG subclasses (IgG1, IgG2, IgG3 IgG4) and three Fc effector function profiles [antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cytotoxicity (ADCC), and antibody-dependent complement deposition (ADCD)] after repeated vaccinations with either NVX-CoV2373 only or after any single rS vaccination following repeated mRNA vaccinations. Total anti-S IgG and IgG1 levels following three homologous doses of mRNA or NVX-CoV2373 were similar, although NVX-CoV2373 induced somewhat higher levels, and the fourth dose of NVX-CoV2373 led to increased responses in each group. Compared with recipients of multiple prior mRNA vaccines, anti-S IgG3 levels were markedly higher (>10-fold) after three or four homologous doses of NVX-CoV2373. By contrast, much higher anti-S IgG4 levels (>75-fold) were observed following repeated mRNA vaccination, but not after three or four homologous doses of NVX-CoV2373. The fourth dose of NVX-CoV2373 also enhanced appeared to enhance surrogate markers for ADCP, ADCC, and ADCD activities in recipients of prior mRNA vaccine, though the effect was greater after a fourth homologous NVX-CoV2373 dose. NVX-CoV2373 did not appear to induce notable increases in IgG4, even after multiple exposures, or to impair the three Fcγ-dependent effector responses as observed with mRNA vaccines. Instead, NVX-CoV2373 drove proportional increases in IgG3, perhaps the most potent SARS-CoV-2 neutralizing antibody subclass, and enhanced surrogate markers for ADCP, ADCD, and ADCC activity. Ongoing investigations of these effects on IgG subclasses and cellular functions are needed to elucidate the immunological diversity generated by different SARS-CoV-2 vaccine platforms. [Kalkeri 2024]

"*Neutralization of SARS-CoV-2 Omicron subvariant BA.2.87.1"* is a short communication that presented results from the authors' evaluation of NAb responses in 34 people (age range 26-73 years) before and after receiving an XBB.1.5 mRNA booster in Fall 2023, to a new SARS-CoV-2 Omicron variant BA.2.87.1, which has over 100 mutations, including more than 30 mutations in the Spike protein compared to BA.2, BA.5, XBB.1.5, and JN.1 variants. The median number of COVID-19 vaccine doses prior to the XBB.1.5 mRNA booster was 4 and nearly three-fourths (71%) of the participants had at least one documented SARS-CoV-2 infection. The vaccination histories for 6 of the 34 individuals comprising the study population included receiving either 2 doses (n=4) or 3 doses (n=2) of NVX-CoV2373, followed by 1-4 doses of original or bivalent mRNA vaccines, or Ad26.COV2.S Janssen COVID-19 viral-vector vaccine, prior to the XBB.1.5 mRNA booster vaccination. The

authors presented aggregate NAb responses to BA.2.87.1, which showed increased NAb titres to all variants tested, including BA.2.87.1. However, NAb responses to the BA.2.87.1 variant were lower than to the BA.2 variant but higher than to JN.1 variant, suggesting that the BA.2.87.1 variant is not a further antibody escape variant compared to other currently circulating variants, such as JN.1. [Lasrado 2024]

"*NVX-CoV2373 induces humoral and cellular immune responses that are functionally comparable to vector and mRNA-based vaccines*" reported the results of the authors' investigation of the immune responses in 42 participants who received one initial dose of NVX-CoV2373 compared to 37 study participants who received either the vector vaccine AZD1222 or the mRNA vaccine BNT162b2 a year earlier. Thirty-two participants also donated blood before their first vaccination to serve as a vaccine-naive control. The authors investigated and quantified the amounts of vaccine-specific antibodies produced at day 21 and approximately six months after primary immunization, their neutralization capacity, their quality in terms of binding different epitopes and their efficiency in inducing antibody isotypes. Cellular immunity and intracellular cytokine production following in vitro re-stimulation with BNT162b2 vaccine was analysed via ELISpot or via flow cytometry. The results showed that vaccination including the mRNA vaccine yielded best results in almost any aspect of antibody levels and binding efficiency, the neutralization capacities against the wild-type Wuhan strain and the Omicron BA.1 variant early and at six months were comparable among all three vaccination groups. As for T cell responses, the authors reported the CD8 response at three weeks which turned into a predominant CD4 memory at six months which was not observed for AZD1222 and BNT162b2. While additional infection with SARS-CoV-2 resulted in a boost for the humoral response, T cell memory appeared rather unaffected. [Mai 2024]

"The humoral and cellular immune responses following booster vaccination with SARS-CoV-2 mRNA in people living with human immunodeficiency virus" presented results from the authors' observational study in Japan of the relationship between HIV status and vaccine-induced immune responses to COVID-19 booster vaccination in 34 adult males (median age 45 years, age range 40–51), following COVID-19 mRNA (n=32) or NVX-CoV2373 (n=2) booster vaccinations. Data were presented for patients as two groups based on the CD4+ T lymphocyte count after their booster vaccination: CD4+ T lymphocytes count of <500/μL (n=14) versus ≥500/μL (n=19, included the two patients who received NVX-CoV2373) at 3 time points: at the time of booster vaccination, 3-12 weeks after booster vaccination and 24 weeks after booster vaccination. Antibody titres for humoral immunity were 50% lower at 24 weeks post-vaccination than at 12 weeks but were approximately eight times higher than before the booster. Regarding cellular immunity, IFN-γ levels at 24 weeks after the third vaccination were lower than those at 12 weeks, but nearly 90% of participants maintained a cut-off value of ≥0.15 IU/mL. All 34 patients met the authors' criterion of vaccine-induced cellular immune response to the SARS-CoV-2 vaccine, defined as an IFN-γ value at least 0.15 IU/mL greater than the negative control. There were no differences in the two groups anti-spike IgG titters and antigen-specific interferon (IFN)-γ levels) over 6 months. [Matsumoto 2024]

"Heterologous SARS-CoV-2 booster vaccine for individuals with haematological malignancies after a primary SARS-CoV-2 mRNA vaccine series" presented results from the authors' prospective cohort study of anti-Spike protein IgG, circulating S protein-specific B cells, and activation induced marker to assess T cell frequencies in peripheral blood samples from 56 adults (≥18 years old) with a history of hematologic malignancy who received the Novavax booster. The cohort was evenly balanced (females, 29/56, 51.8 %, median age 67.3 years, IQR 60.2, 73.2). The most frequent hematologic malignancy was chronic lymphocytic leukemia (n=25, 25/56, 44.6 %). A total of 11/56 (19.6 %) and 9/56 (16.1 %) of participants had undergone allogeneic or autologous hematopoietic stem cell transplant, respectively. The median number of previous mRNA SARS-CoV-2 vaccines received was 5 doses and the median time from last vaccination to the Novavax booster was 6.3 months (IQR 5.5, 6.9). Approximately one-third of participants (20/56, 35.7 %) had a history of prior COVID-19, as determined by positive SARS-CoV-2 PCR or reported history and the median number of days from the most recent SARS-CoV-2 infection to the Novavax booster was 179.5 days (IQR 100.8, 274.5). One month after the Novavax booster vaccination, there was no significant increase in anti-S IgG titres with a modest increase of Spike protein--specific B cells and no significant increase of CD4+ or CD8+ cells. Analysis of blood samples at baseline at Day 28 post-vaccination showed the median fold change of anti-Spike IgG was 1.02 (IQR 0.79, 1.3) between baseline and Day 28 and circulating Spike protein-specific B cells increased 1.4-fold at Day 28 ($p < 0.05$). The authors stated that the increases in antibody and T cell responses were modest without significance and that humoral and cellular immune responses waned at 168 days post-vaccination. [Sherman 2024]

18 INTEGRATED BENEFIT-RISK ANALYSIS

18.1 Benefit-Risk Context - Medical Need and Important Alternatives

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. The virus rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In Feb-2020, the WHO designated the disease coronavirus disease 2019 or COVID-19. The virus that causes COVID-19 was designated SARS-CoV-2.

It has been 4.5 years since the WHO declared COVID-19 was a global pandemic. As of 23-Jun-2024, there were more than 775 million confirmed cases of COVID-19 worldwide and more than 7 million deaths worldwide [WHO 2024]. The reported case counts underestimate the overall burden of SARS-CoV-2, as only a fraction of acute infections is diagnosed and reported. Seroprevalence surveys in the US and Europe suggested that after accounting for potential false positives or negatives, the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, may exceed the incidence of reported cases by approximately 10-fold or more [Stringhini 2020, Havers 2020].

To date, several vaccines have been authorized in multiple countries globally for the prevention of COVID-19. Despite these preventative measures and treatments, there remains an unmet medical need. While multiple vaccines for the prevention of COVID-19 continue in

development, the National Institutes of Health (NIH) has reported that more than one effective vaccine approach likely will be needed to successfully protect the global community from SARS-CoV-2, emphasizing that no single vaccine or vaccine platform is likely to meet the global need [NIH 2020]. Novavax's SARS-CoV-2 rS vaccine adjuvanted with Matrix-M is one such platform.

Treatment Options:

Management of Persons with COVID-19:

Management of COVID-19 is based on the best supportive care and emerging standard of care. Medications authorised for treatment of COVID-19 in the EU include antiviral medicines (i.e., Paxlovid and Veklury), monoclonal antibodies (i.e., Evusheld, Regkirona, RoActemra, Ronapreve, Xevudy), and an immunosuppressive medicine (Kineret) [EMA 2024a].

Prophylaxis:

The following vaccines are authorized for use in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus: Comirnaty (BioNTech and Pfizer), Spikevax (Moderna), Nuvaxovid (Novavax), Jcovden (Janssen), and Bimervax (HIPRA Human Health) [EMA 2024b].

In addition, two monoclonal antibodies, Evusheld and Ronapreve, are authorised for prevention of COVID-19 [EMA 2024a]. General preventative measures include social distancing, face masks, and proper hygiene.

18.2 Benefit-Risk Analysis Evaluation

It has been 4 years since SARS-CoV-2 was declared a global pandemic by the WHO. Several vaccines against the prototype Wuhan-Hu-1 strain had received authorizations/approvals globally as of late 2020/early 2021. Despite this vaccination number, there remains a large global need for additional vaccine doses, including vaccines efficacious against the evolving variants and having more readily satisfied storage conditions and stability.

In adult participants ≥ 18 years of age following primary series vaccination, NVX-CoV2373 demonstrated efficacy of ~90% in the pivotal Phase 3 study following primary vaccination, with comparable efficacy against variants that were either considered VOC/VOI or not considered VOC/VOI. Among NVX-CoV2373 adult recipients, there were no cases of severe disease with an onset from at least 7 days after second vaccination in the pivotal Phase 3 study. The clinical benefit of NVX-CoV2373 was consistent among, males and females, White and non-White, Black or African Americans, and those with co-morbidities or at high-risk of being exposed or infected with SARS-CoV-2. The results of the pivotal efficacy study demonstrating ~90% efficacy against mild, moderate, or severe COVID-19, as well as 100% efficacy against severe disease, are supported by the robust immune responses observed in the

pivotal Phase 3 study. In older adults, neutralizing antibody responses would have met the GMT non-inferiority criterion compared to adults 50 to < 65 years of age, an age group in which there were sufficient cases of COVID-19 to establish efficacy.

In adolescent participants 12 to < 18 years of age, based on the results of the Paediatric Expansion of the pivotal Phase 3 study 2019nCoV-301, NVX-CoV2373 met the criteria to establish its effectiveness by demonstrating non-inferiority of the neutralizing antibody response in adolescent participants 12 to < 18 years of age compared to young adults 18 to < 26 years of age following primary series vaccination. For the primary efficacy endpoint, the vaccine efficacy of NVX-CoV2373 for preventing symptomatic mild, moderate, or severe COVID-19 in baseline seronegative/ PCR-negative-adolescent participants was ~80% during a period in which the B.1.617.2 (Delta) variant was predominant. NVX-CoV2373 also generated robust immune responses (neutralizing antibody and anti-S protein IgG) relative to placebo in adolescent participants 12 to < 18 years of age regardless of baseline serostatus.

Based on the administration of NVX-CoV2373 to 26,106 adults in the Adult Main study of Clinical Study 2019nCoV-301 across the initial and blinded crossover vaccination periods, with 13,353 participants receiving a booster vaccination and an additional 15,440 participants across the supportive clinical studies in the SARS-CoV-2 rS clinical development program and 2,153 adolescents in the Paediatric Expansion of Clinical Study 2019nCoV-301 across the initial and blinded crossover vaccination periods, with 1,499 participants receiving a booster vaccination, following primary series vaccination or a heterologous/homologous booster vaccination, the safety profile has been largely characterized by mild or moderate reactogenicity reactions of short duration (median duration of 2 days). Most common among these reactions were tenderness and pain at the injection site and systemic events of fatigue, muscle pain, headache, joint pain, and malaise. Although the incidence of unsolicited TEAEs in adult participants and of unsolicited treatment-related TEAEs in both adult and adolescent participants was slightly higher in the NVX-CoV2373 group than in the placebo group, the difference was largely due to reactogenicity-like events. SAEs and deaths (adults only) occurred in few participants, with similar events for placebo and vaccine recipients that were generally balanced across treatment groups for both adults and adolescents. These findings are further supported with the data from the Integrated Safety Summary, which comprised 31,479 adult participants and 1,487 adolescent participants in the NVX-CoV2373 groups who received study vaccine at the start of each clinical study.

Based on post-authorization reports, anaphylaxis, paresthesia/hypoesthesia, and myocarditis and/or pericarditis are considered identified risks for the Biologics License Application submission.

Based on the totality of the data across the SARS-CoV-2 rS clinical development program, the Novavax COVID-19 vaccines administered as either 2 intramuscular injections at least 21 days (+ 7 days) apart as primary series vaccination or as 1 intramuscular injection in previously vaccinated individuals is an effective vaccine with an acceptable safety profile for

the active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in both adults ≥ 18 years of age and adolescents 12 to < 18 years of age. Homologous booster vaccination in adult and adolescent participants induced robust immune responses that exceeded those reported following primary series vaccination. Heterologous booster vaccination in adult participants also resulted in robust increases in neutralizing antibody titers.

It is important to note that the dose of the Novavax COVID-19 vaccines for both primary and booster injections is the same for all ages, thus facilitating ease of use for vaccine administrators and reducing the likelihood of dosing errors.

Considering the endemicity of SARS-CoV-2, emergence of new antigenic variants, and the need for additional effective vaccine options, along with the available efficacy/effectiveness, immunogenicity, and safety data across the SARS-CoV-2 rS clinical development program, NVX considers that the known and potential benefits outweigh the known and potential risks of the Novavax COVID-19 vaccines and support authorization for individuals ≥ 12 years of age for primary series vaccination and for periodic revaccination.

19 CONCLUSION

During the reporting interval, no signals were generated through O/E monitoring of AESIs. Two new signals of migraine and tachycardia were validated following health authority requests from TGA and FDA respectively. Both signals were refuted upon evaluation.

The final disposition of a previously validated signal of tinnitus was updated to refuted during the reporting interval in response to US FDA and EMA reviews and assessments. Tinnitus has been removed from the adverse reactions from post-marketing experience section (Section 4.8) of the CCDS v10.0, effective 30-May-2024 and will remain in the post authorisation section of the Australian Product Information (Section 4.8). Events of tinnitus will continue to be monitored under routine pharmacovigilance.

Cumulatively, signals of anaphylaxis, paraesthesia, and myopericarditis, myocarditis and pericarditis have been confirmed, and the CCDS has been updated to include paraesthesia/hypoaesthesia in Section 4.8 (Undesirable effects) of v5.0 dated 21-Jul-2022. Anaphylaxis and myocarditis and pericarditis were added to Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 of the CCDS v5.0 dated 21-Jul-2022 and v6.0 dated 10-Aug-2022 respectively.

During the reporting interval, NVX received marketing authorisation for Covovax in Brazil as a primary series for individuals 12 years and older and for Nuvaxovid in Japan as a primary series for individuals 6 years and older. Additionally, Nuvaxovid XBB.1.5 received marketing authorisation for individuals 12 years and older in UK and Covovax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) received approval in Brazil.

The clinical evidence and post-authorisation safety data collected as of the DLP of this report support the safety and efficacy of Nuvaxovid. Analysis of the data contained within this report supports the adequacy of the current RSI (CCDS v10.0, dated 30-May-2024) for Nuvaxovid and Nuvaxovid XBB.1.5 and support the conclusion that the overall benefit-risk balance for Nuvaxovid and Nuvaxovid XBB.1.5 continues to remain positive.

NVX will continue to monitor the safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines.

20 APPENDICES