Nuvaxovid: Periodic safety update report assessment

20 June 2024 to 19 December 2024

This document consists of:

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

EMADOC-1700519818-1988260
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000257887

PRAC PSUR assessment report

EURD list no.: PSUSA/00010972/202412

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: 6 months to 19 December 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

Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	12 March 2025	12 March 2025
☐	Start date	13 March 2025	13 March 2025
☐	PRAC Rapporteur AR	12 May 2025	02 April 2024
☐	PRAC/MAH comments	11 June 2025	11 June 2025
☐	Updated PRAC Rapporteur AR	26 June 2025	n/a
☒	PRAC outcome	10 July 2025	10 July 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 Assistance, pharmacovigilance inspections) , irrespective from which entity this was received*.

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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 6th periodic benefit-risk evaluation report (PBRER)/periodic safety update report (PSUR) for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1, 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 subvariant, has been authorised in the European Union (EU) on 31 October 2023. The updated vaccine for the Omicron JN.1 subvariant, Nuvaxovid JN.1, has been authorised in the EU on 08 October 2024. This PSUR covers the 6-month interval between 20 June 2024 and 19 December 2024, with the data lock point (DLP) 19 December 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.

According to the MAH, clinical trial exposure comprises a cumulative total of 49,962 participants exposed to at least one dose of SARS-CoV-2 recombinant, adjuvanted vaccines, either monovalent or bivalent, prototype or variant. A total of 5,625 participants were engaged in blinded treatment arms of studies across the MAH-sponsored SARS-CoV-2 rS and COVID-19 influenza combination clinical development programs. An additional 1,422 participants were exposed to the prototype SARS-CoV-2 rS vaccine in two MAH-sponsored clinical trials involving a COVID-19 influenza combination vaccine. Post authorisation, a total of 715,139 and 4,907,317 doses of Novavax COVID-19 vaccines are estimated to have been administered during the reporting interval and cumulatively (Nuvaxovid, 1,608 and 2,990,785 doses; Nuvaxovid XBB.1.5, 9,888 and 1,212,889 doses; Nuvaxovid JN.1, 703,643 doses during the reporting interval and cumulatively).

No new signals were validated during the reporting interval. The signals of anaphylaxis, myopericarditis/myocarditis/pericarditis and paraesthesia 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, migraine, oculomotor cranial nerve disorders, sensorineural hearing loss, syncope, tachycardia, tachycardia and other rhythm disorders, and tinnitus.

During the reporting interval, the MAH did not identify any new important risks or any new significant information related to existing risks. The EU risk management plan (RMP) was updated to version 6.1, dated 31 October 2024, to support the prefilled syringe presentation of the JN.1 variant-adapted vaccine. There were no changes to the list of 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, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

In its cover letter, the MAH proposes to (i) discontinue observed-to-expected (O/E) analyses for signal generation and leverage O/E analyses going forward for signal clarification, consistent with guidance for non-pandemic periods and in the absence of large influxes of data from mass immunisation programs, and (ii) to maintain adverse events of special interest (AESI) within the Nuvaxovid surveillance plan and provide descriptive, cumulative analyses in PSUR for those AESI with new validated signals going forward. Both proposals are considered acceptable.

All in all, the safety profile of Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 remains within the expected scope. The data provided by the MAH does not alter previous assessments of efficacy or effectiveness. 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 XBB.1.5, Nuvaxovid JN.1) remains unchanged in its authorised indications.

As concluded in procedure EMEA/H/C/PSUSA/00010972/202406, the PSUR interval will be extended from 6 months to 1 year.

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 XBB.1.5, Nuvaxovid JN.1) remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. PSUR frequency

☒No changes to the PSUR frequency

The current **1**-year frequency for the submission of PSURs should remain unchanged.

Annex: preliminary PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

Abbreviations

ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
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
DIBD	development international birth date
DLP	data lock point
EMA	European Medicines Agency
EU	European Union
EURD	European Union reference date
IBD	international birth date
ICSR(s)	individual case safety report(s)
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
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
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT(s)	preferred term(s)
r	recombinant
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
SOC(s)	system organ class(es)
UK	United Kingdom
US	United States
WHO	World Health Organisation

1.1. Introduction

This 6th periodic safety update report (PSUR) for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 covers the 6-month interval between 20 June 2024 and 19 December 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 Omicron JN.1, respectively. Currently three of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373), Nuvaxovid XBB.1.5 (NVX-CoV2601) and Nuvaxovid JN.1 (NVX-CoV2705).

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, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 are used when referring to these vaccines in the post-authorisation setting, while the study vaccine names NVX-CoV2373 (or prototype), NVX-CoV2601 and NVXCoV2705 are used when referring to these vaccines in clinical trials.

Table 1: Vaccines Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 (PSUR pp. 5 and 28)

Parameters	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Vaccine code	NVX-CoV2373	NVX-CoV2601	NVX-CoV2705
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5	SARS-CoV-2 Omicron variant lineage JN.1
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 vials containing either 5 or 10 doses per vial [1]	Single or Multidose vials Multi-Dose vial containing 5 doses per vial	Single-dose vials [2]
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. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.	Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations

[1] Nuvaxovid is also approved as prefilled syringes in South Korea.
[2] Nuvaxovid JN.1 is also approved as prefilled syringes (US and South Korea) and as multi-dose vials in other regions.

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 3 (Table 30, pp. 338-343), Nuvaxovid was first authorised in Indonesia on 31 October 2021 (Covovax). Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 were first authorised in the United States (US) on 03 October 2023 (Novavax COVID-19 vaccine, adjuvanted [2023-2024 formula]; PSUR Appendix 3, Table 31, p. 344) and on 30 August 2024 (Novavax COVID-19 vaccine, adjuvanted [2024-2025 formula]; PSUR Appendix 3, Table 32, p. 345), respectively. In the EU, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 were authorised on 20 December 2021, 31 October 2023 and 08 October 2024, 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. In Switzerland, the approval of Nuvaxovid was withdrawn on 21 March 2024.

Table 2: Nuvaxovid – invented names and countries/region of authorisation (adapted from PSUR Appendix 3, Table 30, pp. 338-343). 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 several 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 another marketing authorisation in Taiwan, and Novavax COVID-19 vaccine, adjuvanted (2023-2024 formula) was withdrawn in the US, in parallel with the authorisation of Novavax COVID-19 vaccine, adjuvanted (2024-2025 formula).

Table 3: Nuvaxovid XBB.1.5 – invented names and countries/region of authorisation (adapted from PSUR Appendix 3, Table 31, p. 344). UK, United Kingdom; WHO, World Health Organisation.

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

Nuvaxovid JN.1: Nuvaxovid JN.1 received authorisation for emergency use or marketing authorisation for individuals 12 years and older in several countries and the EU region. An alternative name is Novavax COVID-19 vaccine, adjuvanted (2024-2025 formula) in the US. During the reporting interval, Novavax COVID-19 Vaccine, adjuvanted (2024-2025 formula) received emergency use authorisation in the US and South Korea, and Nuvaxovid JN.1 received authorisation in Canada, EU, Japan, Singapore and the United Kingdom.

Table 4: Nuvaxovid JN.1 – invented names and countries/region of authorisation (adapted from PSUR Appendix 3, Table 32, p. 345). UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Novavax COVID-19 vaccine, adjuvanted (2024-2025 formula)	South Korea, US
Nuvaxovid	Canada, Japan, Singapore, UK
Nuvaxovid JN.1	EU

The MAH notes that authorisations are pending in other regions.

Rapporteur assessment comment:

During the reporting interval, Novavax COVID-19 vaccine, adjuvanted (2024-2025 formula) received emergency use authorisation in the US and in South Korea. Nuvaxovid JN.1 received authorisation in Canada, the EU, Japan, Singapore and the UK. Since the authorisation of the updated vaccine, the prototype vaccine and the 2023-2024 formula are no longer authorised in the US (30 August 2024).

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 and at the end of the reporting interval was the company core data sheet (CCDS) version 10.0, dated 30 May 2024. No updates were made to the CCDS during the reporting interval.

During the reporting interval, the MAH submitted the following safety variation and received approval: Removal of tinnitus from the Health Canada Product Monograph.

Rapporteur assessment comment:

CCDS version 10.0 is used as RSI, and no updates were made during the reporting interval.

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

According to the MAH, clinical trial exposure comprises a cumulative total of 49,962 participants exposed to at least one dose of its SARS-CoV-2 vaccines, either monovalent or bivalent, prototype or variant. A total of 5,625 participants were engaged in blinded treatment arms of studies across the MAH-sponsored SARS-CoV-2rS and COVID-19 influenza combination clinical development programs. An additional 1,422 participants were exposed to the prototype SARS-CoV-2 rS vaccine in two MAH-sponsored clinical trials involving a COVID-19 influenza combination vaccine.

The MAH's COVID-19 vaccines include the monovalent vaccines prototype (NVX-CoV2373; n = 46,776 participants exposed in clinical trials), BA.1 (NVX-CoV2515; n = 347), BA.5 (NVX-CoV2540; n = 297), XBB.1.5 (NVX-CoV2601; n = 1,671), and JN.1 (NVX-CoV2705; n = 60); 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; n = 210); and the COVID-19 and influenza combination (CIC) vaccines prototype (NVX-CoV2373) + quadrivalent nanoparticle influenza vaccine (n = 1,422) and JN.1 (NVX-CoV2705) + trivalent nanoparticle influenza vaccine (n = 1,985 participants who received blinded treatment). A total of 5,625 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 3 and 4, p. 37) and by racial group (PSUR Table 5, p. 38). A total of 2,557 individuals from 12 to < 18 years of age were exposed to the vaccines. Participants under 12 years of age received blinded treatment only (6 to < 24 months, n = 1,164; 2 to < 6 years, n = 1,216; 6 to < 12 years, n = 1,260). A total of 8,288 subjects > 65 years received the COVID-19 vaccines or blinded treatment.

Rapporteur assessment comment:

According to PSUR Table 2, a total of 56,936 participants (147 participants from 2019nCoV-312 study counted twice; 220 participants from 2019nCoV-415 study excluded) were exposed to at least one

dose of Novavax COVID-19 vaccines or blinded treatment. According to the data provided, predominantly adults were included in clinical trials with the vaccines (18-65 years, n = 42,451, including participants exposed to blinded treatment and subjects from study 2019nCoV-312 counted twice, excluding participants from 2019nCoV-415 study). The sex distribution of the participants is quite balanced, and the majority of subjects are described as White or Caucasian (n = 40,049).

Post-authorisation exposure

The MAH notes that it does not have access to data regarding post-authorisation use in special populations. At this time, post-authorisation safety studies with Novavax COVID-19 vaccines are not sufficiently powered to provide any information on exposure in special populations.

Table 5: Summary of interval and cumulative administration data of Novavax COVID-19 vaccines (PSUR pp. 7 and 39)

Timeframe	Nuvaxovid [2]	Nuvaxovid XBB.1.5 [2]	Nuvaxovid JN.1	Novavax COVID-19 Vaccines
Interval [1]	1,608	9,888	703,643	715,139
Cumulative	2,990,785	1,212,889	703,643	4,907,317

[1] Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source.

[2] Includes Novavax and Serum Institute of India Pvt Ltd. (SIIPL) products corresponding to the Novavax COVID-19 vaccines.

Table 6: Summary of interval and cumulative distribution data of Novavax COVID-19 vaccines (PSUR Appendix 10, Table 42, p. 542)

Time Frame	Nuvaxovid [2]	Nuvaxovid XBB.1.5	Nuvaxovid JN.1	Novavax COVID-19 Vaccines
Interval [1]	0	28,600	4,937,992	4,966,592
Cumulative	115,971,670	17,969,000	4,937,992	138,878,662

[1] Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source as indicated in Table 41.

[2] Includes both Nuvaxovid and SIIPL products corresponding to the original and updated Novavax COVID-19 vaccines.

Table 7: Interval and cumulative estimated exposure data of Novavax COVID-19 vaccines by dose (PSUR Appendix 10, Table 44, pp. 545-546)

Timeframe/Formulation	Dose	Doses Administered (per received data) [1]	Adjusted Doses Including Re-allocated Doses (from unknown dose number or unknown vaccine) [2]	Calculated Doses Administered [3]	Total Estimated Doses Administered [4]
Interval					
Nuvaxovid	First Dose	87	87	0	87
	Second Dose	36	36	0	36
	Booster Dose	1,485	1,485	0	1,485
	Unknown Dose number	0	0	0	0
Nuvaxovid XBB.1.5 [f]	First Dose	240	240	0	240
	Second Dose	333	333	0	333
	Booster Dose	9,315	9,315	0	9,315
	Unknown Dose number	0	0	0	0
Nuvaxovid JN.1 [f]	First Dose	0	0	0	0
	Second Dose	0	0	0	0
	Booster Dose	703,643	703,643	0	703,643
	Unknown Dose number	0	0	0	0
	Interval Total [5]	**715,139**	**715,141**	**0**	**715,141**
Cumulative					
Nuvaxovid	First Dose	650,363	689,422	12,106	701,528
	Second Dose	514,927	540,030	6,413	546,443
	Booster Dose	1,822,722	1,831,041	2,841	1,833,882
	Unknown Dose number	13	0	0	0
Nuvaxovid XBB.1.5 [6]	First Dose	559	559	0	559
	Second Dose	337	337	0	337
	Booster Dose	1,211,993	1,211,993	0	1,211,993
	Unknown Dose number	0	0	0	0
Nuvaxovid JN.1 [6]	First Dose	0	0	0	0
	Second Dose	0	0	0	0
	Booster Dose	703,643	703,643	0	703,643
	Unknown Dose number	0	0	0	0
	Cumulative Total [5]	**4,907,317**	**4,979,792**	**21,356**	**5,001,148**

NOTE: Data sources and cut off dates are presented in Table 41 above. The total number of doses administered column may not add to the number of individuals as individuals may receive more than 3 doses.

[1] Data presented as recorded. No assumptions or adjustments were made regarding this data. All countries with administration data are presented in this column. Please refer to Table 41 for a list of countries with administration data.

[2] Column represents administration data re-allocated to first, second and booster dose only (refer to calculations above Table 44. This column accounts for unknown dose as well as unknown vaccine. Unknown vaccines doses are re-allocated to Novavax vaccine using the proportion of Novavax vaccine among the total doses administered. All countries with administration data according to Table 41 are presented in this column. For a list of countries this re-allocation applied to, please refer to text above Table 44.

[3] Column represents derived administration doses. This was only done for countries without administration data during this interval. Assumptions applied to derive administered dose are presented in the text above Table 44 and on Table 44.

[4] Column represents all estimated administration doses including all countries. This column is a summation of third and fourth columns. All countries with either administration data or derived administration data are represented in this column.

[5] The interval and cumulative total is not consistent with the sum of the individual dosing because part of the data presented represents the raw source data provided by Australia and New Zealand which has a total dose that is higher than the sum of Dose 1, Dose 2 and booster. Due to the raw data from these two countries the total dose is higher than the sum of the columns.

[6] All doses of the Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 vaccines are allocated to booster dose if there is no stratified dose number data available.

Administration data stratified by age group for Nuvaxovid and Nuvaxovid XBB.1.5 are provided for countries and regions that provide exposure by age category including Australia, the EU, New Zealand (until 31 December 2022), South Korea (until 27 February 2024), Japan, Switzerland, and UK. The results reflect direct summation from these regions only; no extrapolations have been made. Age stratified administration data is not available for Nuvaxovid JN.1.

Table 8: Interval and cumulative administration data of Novavax COVID-19 vaccines by age group (PSUR Appendix 10, Table 46, p. 548)

Total Doses Actually Administered [1,2,3,4]						
Dose	**Nuvaxovid**			**Nuvaxovid XBB.1.5**		
	Paediatrics	**Adults**	**Elderly**	**Paediatrics**	**Adults**	**Elderly**
Interval						
First Dose	0	0	0	0	0	0
Second Dose	0	0	0	0	0	0
Third/Booster Dose	0	0	0	0	0	0
Unknown Dose	0	0	0	0	0	0
Interval Total	0	0	0	0	0	0
Cumulative						
First Dose	188	94,073	18,086	0	0	0
Second Dose	184	55,590	14,285	0	0	0
Third/Booster Dose	191	36,055	35,237	8,928	378,857	378,189
Unknown Dose	2,040	200,117	71,521	0	0	0
Cumulative Total	2,603	385,835	139,129	8,928	378,857	378,189

[1] Data presented as recorded. The list of countries that included age data within the available administration data are presented in the text above this table up to the cut-off date indicated in Table 41 above, with the exception of New Zealand as age stratified data is only available until 31-Dec-2022 and South Korea as age stratified data is only available until 27-Feb-2024.

[2] Some countries in EU did not provide age categories consistently as per ECDC data, so this table does not cover all doses from ECDC data.

[3] Age groups under the available age stratification for the EU and New Zealand is as follows: Paediatric < 18 years; adults 18 – 69 years; elderly 70 + years. Age stratification of South Korea was: Paediatric 12 – 17 years; adults 18 – 64 years; elderly 65+ years. Age stratification of Switzerland was: Paediatric ≤ 19 years; adults: 20 – 69 years; elderly: 70 + years and Japan stratified elderly as 65+ years. Age stratification of Australia was: Paediatric < 18 years; adults 18 – 64 years; elderly 65 + years.

[4] New Zealand had administration data for only adolescent and elderly age groups. Japan had administration data for only elderly age groups (65+ years).

Rapporteur assessment comment:

According to Table 6 (PSUR p. 39), a total of 715,139 and 4,907,317 doses of Novavax COVID-19 vaccines are estimated to have been administered during the reporting interval and cumulatively (Nuvaxovid, 1,608 and 2,990,785 doses; Nuvaxovid XBB.1.5, 9,888 and 1,212,889 doses; Nuvaxovid JN.1, 703,643 doses during the reporting interval and cumulatively). According to Appendix 10, Table 44 (PSUR pp. 545-546), most of the doses are estimated to have been administered as booster doses.

1.3.4. Data in summary tabulations

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 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 4 (Appendix 4A, PSUR pp. 347-369; Appendix 4B, PSUR pp. 370-382), the MAH presents cumulative summary tabulations of treatment-emergent SAEs from MAH-sponsored interventional clinical trials of NVX-CoV2373, NVX-CoV2515, NVX-CoV2540, NVX-CoV2601 and NVX-CoV2705 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 5A (PSUR pp. 384-442), 5B (PSUR pp. 443-461) and 5C (PSUR pp. 462-478) for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1, respectively.

Table 9: Overview of interval and cumulative individual case safety reports (ICSRs) and adverse events (AEs) for Novavax COVID-19 vaccines (PSUR p. 43)

Parameters		Nuvaxovid (Cumulative Administered Doses = 2,990,785)		Nuvaxovid XBB.1.5 (Cumulative Administered Doses = 1,212,889)		Nuvaxovid JN.1 (Cumulative Administered Doses = 703,643)	
		Interval [1]	Cumulative	Interval [1]	Cumulative	Interval [1]	Cumulative
Number of ICSRs		98 (50 initial, 48 follow-up)	5,198	123 (111 initial, 12 follow-up)	613	361 (initial)	361
Serious ICSRs (including fatal)		30	1,028	22	86	56	56
Non-Serious ICSRs		68	4,170	101	527	305	305
Fatal ICSRs		1 (initial)	35	1 (follow-up)	8	5 (initial)	5
Number of AEs		352	18,567	303	2,147	1003	1003
Serious AEs		116	2,923	48	211	141	141
Non-serious AEs		236	15,644	255	1,936	862	862
Number of ICSRs classified by age group	Foetus [2]	1	1	1	3	–	–
	Neonate [2]	–	3	–	1	–	–
	Infant [3]	–	1	1	1	–	–
	Child	–	8	–	2	2	2
	Adolescent	7	66	–	5	13	13
	Adult	56	3,759	29	187	143	143
	Elderly	10	734	18	112	121	121
	Unknown	24	626	74	302	82	82

[1] Includes both initial and follow-up ICSRs.
[2] Secondary exposure during pregnancy.
[3] Off-label use.

The overall Nuvaxovid adverse event reporting rate has decreased over time and with the introduction of variant-adapted vaccines from 0.17 to 0.05 individual case safety reports (ICSRs) per 100 doses.

A total of 5,198 ICSRs were reported with Nuvaxovid corresponding to a reporting rate of 0.17 ICSR per 100 vaccinations (5,198/2,990,785 doses administered). The most frequently reported AEs fall under MedDRA system organ classes (SOCs) General disorders and administration site conditions (n = 5,327 AEs; preferred term [PT] Fatigue, n = 704), Nervous system disorders (n = 3,113; PT Headache, n = 1,067), Musculoskeletal and connective tissue disorders (n = 2,028; PT Myalgia, n = 712), Gastrointestinal disorders (n = 1,213; PT Nausea, n = 472), and Skin and subcutaneous tissue disorders (n = 1,065; PT Rash, n = 292).

A total of 613 ICSRs were reported with Nuvaxovid XBB.1.5, corresponding to a reporting rate of 0.05 ICSR per 100 vaccinations (613/1,212,889 doses administered). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n = 808 AEs, PT Fatigue, n = 123), Musculoskeletal and connective tissue disorders (n = 274; PT Myalgia, n = 93), Nervous system disorders (n = 257; PT Headache, n = 117), Injury, poisoning and procedural complications (n = 173; PT Expired product administered, n = 39), and Gastrointestinal disorders (n = 143; PT Nausea, n = 62).

A total of 361 ICSRs were reported with Nuvaxovid JN.1, corresponding to a reporting rate of 0.05 ICSR per 100 vaccinations (361/703,643 doses administered). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n = 315 AEs; PT Pyrexia, n = 36), Nervous system disorders (n = 154; PT Headache, n = 39), Musculoskeletal and connective tissue disorders (n = 112; PT Pain in extremity, n = 38), Injury, poisoning and procedural complications (n = 89; PT Expired product administered, n = 33), and Gastrointestinal disorders (n = 64; PT Nausea, n = 23).

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 191), covering the period from 26 February 2021 to 27 October 2024. As per the report, a cumulative total of 974,574 Nuvaxovid doses were administered with a corresponding total of 1,298 ICSRs reported; a total of 12,312 doses of Novavax COVID-19 vaccine 2023-2024 formula with a corresponding total of 4 ICSRs reported; and a total of 65,262 doses of Novavax COVID-19 vaccine adjuvanted (2024-2025 formula) with no ICSRs reported. The most frequently reported symptoms suspected to be AEs were myalgia (n = 279), headache (n = 260), dizziness (n = 180), allergic reaction (n = 173), chest pain (n = 172) and vaccination site pain, rash, swelling within 3 days of vaccination (n = 138). A cumulative total of 13 cases reported fatal outcomes; no new fatal events were reported during the reporting interval.

Rapporteur assessment comment:

The presentation of SAEs from clinical studies, broken down by study product and type of vaccine, is appreciated. Appendix 4B lists a total of 3,059 SAEs – 172 reported with blinded treatment, 12 with comparator products, 2,303 with placebo/vehicle and 2,584 with Novavax COVID-19 vaccines. The SOCs under which SAEs were most frequently reported were Infections and infestations (n = 738), Cardiac disorders (n = 326) and Injury, poisoning and procedural complications (n = 278).

Adverse reactions from post-authorisation data sources are presented separately for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1. Appendix 5A lists a cumulative total of 18,337 spontaneously reported events for Nuvaxovid, thereof 2,915 serious and 15,422 non-serious events (reporting interval, 121 serious and 213 non-serious events). In addition, 7 serious events were reported cumulatively from non-interventional post-marketing study and other solicited sources (reporting interval, no serious event). Appendix 5B lists a cumulative total of 1,431 spontaneously reported events for Nuvaxovid XBB.1.5, thereof 207 serious and 1,224 non-serious events (reporting interval, 46 serious and 253 non-serious events). In addition, 4 serious events were reported cumulatively from non-interventional post-marketing study and other solicited sources (reporting interval, 2 serious events). Appendix 5 C lists a total of 985 spontaneously reported events for Nuvaxovid JN.1, thereof 141 serious and 844 non-serious events for the reporting interval and cumulatively. No serious event was reported from non-interventional post-marketing study and other solicited sources.

The adverse event reporting rate was higher for Nuvaxovid than for Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 – 0.17 ICSRs per 100 vaccinations (5,198/2,990,785 doses administered) versus 0.05 ICSRs per 100 vaccinations (613/1,212,889 doses administered) and 0.05 ICSRs per 100 vaccinations (361/703,643 doses administered), 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 (2019nCoV-301 Adolescent Main and Adolescent Booster), one part of a 2-part clinical trial (2019nCoV-311 Part 2) and three other clinical trials (2019nCoV-312, 2019nCoV-313 [Parts 1 and 2] and 2019nCoV-314) were completed. As of the DLP (19 December 2024), four MAH-sponsored clinical trials (2019nCoV-205, 2019nCoV-315, 2019nCoV-415 and 2019nCoV-503) were ongoing. Participants in MAH-sponsored clinical trials were either adults (≥ 18 years), adolescents (≥ 12 years to < 18 years) or paediatric (6 months to < 12 years).

Completed clinical trials

The MAH states that no new clinically important safety information emerged from the below trials during the reporting interval.

Study 2019nCoV-301 Adolescent Primary Series (Main) and Adolescent Booster. Study 2019nCoV-301 was a phase 3, multinational, multicentre, randomised, observer-blinded, placebo-controlled study evaluating the efficacy, effectiveness, safety, and immunogenicity of 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 in the US. This study also included a Booster Amendment and Second Booster Vaccination Sub-study, which allowed for the evaluation of first and second booster doses of NVX-CoV2373, respectively. Approximately 3,000 adolescent participants were randomised in a 2:1 ratio via block randomisation to receive 2 intramuscular injections of NVX-CoV2373 or placebo (normal saline). The efficacy demonstrated across most demographic subsets of the efficacy population was similar to the overall Per Protocol Efficacy population. The safety of both the primary vaccination series and the booster injections, in terms of solicited as well as unsolicited treatment emergent adverse events was similar to that described in adults in this and other clinical trials.

Study 2019nCoV-311 Part 2 – 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 (764 participants exposed). Study part 2 evaluated the immunogenicity and safety of 2 booster doses of NVX-CoV2540 and NVX-CoV2373 alone and bivalent prototype and Omicron BA.5 subvariant vaccine in previously vaccinated (i.e., ≥ 3 doses of the Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines) in adults ≥ 18 years of age. Each of the three co-primary endpoints was achieved, demonstrating that the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induced superior neutralising antibody responses compared to the prototype NVX-CoV2373 vaccine in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA COVID-19 vaccines. NVX-CoV2540, NVX-CoV2373, and NVX-CoV2373 + NVX-CoV2540 were well tolerated with an acceptable safety profile after booster vaccination in adult participants who had previously received ≥ 3 vaccinations of Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines.

Study 2019nCoV-312 – A phase 3 study to evaluate the immunogenicity and safety of Novavax COVID-19 vaccine(s) as second or subsequent boosters after mRNA vaccines in individuals 18 to 49 years of age (147 participants exposed). Study 2019nCoV-312 was an open-label study evaluating the immunogenicity and safety of Novavax vaccine(s) with Matrix-M adjuvant (ancestral strain NVX-CoV2373 and an alternative strain and/or multivalent Novavax vaccine) as booster doses following a series of primary and/or booster doses of authorised/approved mRNA vaccines followed by a single booster dose of NVX-CoV2373 in the Novavax 2019nCoV-307 study (Study 307). Approximately 100 participants received one dose of the ancestral strain NVX-CoV2373 vaccine, and approximately 50 additional participants were enrolled to receive one dose of the updated vaccine NVX-CoV2540. The study met the primary endpoints; when Day 29 immunogenicity results for participants who received a booster dose of NVX-CoV2373 in Study 312 compared to results in Study 307, the primary endpoints of non-inferiority and superiority were met. For the participants who received the updated vaccine (NVX-CoV2540, Omicron BA.5), non-inferiority and superiority between booster doses at Day 29 from Study 312 and Study 307 were demonstrated as a descriptive endpoint. Both NVX-CoV2373 and NVX-CoV2540 were found to have an acceptable safety profile in this study.

Study 2019nCoV-313 Part 1. Study 2019nCoV-313 was a 2-part, phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 in adult participants ≥ 18 years of age (Part 1; 332 participants exposed) previously vaccinated with

messenger ribonucleic acid (mRNA) COVID-19 vaccine and in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants ≥ 18 years of age (Part 2; 338 participants exposed) in the US and its territories. Participants received booster vaccination on Day 0 and were followed for immunogenicity and safety data collection through Day 180 with interim analyses planned at Day 28. 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 NVX-CoV2373 (data derived from Group G of Part 2 of Study 2019nCoV-311 conducted in Australia approximately 6 months prior to the start of Study 2019nCoV-313) and (2) to determine if NVX-CoV2601 booster induced noninferior seroresponse rates compared to seroresponse rates of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations. A total of 332 participants were enrolled in the study at 30 sites in the US and its territories. Data from one site was not used in any of the analyses due to data compliance issues. Both co-primary endpoints were achieved. NVX-CoV2601 was well tolerated with an acceptable safety profile following booster vaccination in adult participants ≥ 18 years of age who had previously received ≥ 3 mRNA prototype COVID-19 mRNA vaccines.

Study 2019nCoV-313 Part 2. The co-primary objectives in Part 2 were (1) to determine if a single dose of NVX-CoV2601 in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induced noninferior seroresponse rates to the Omicron XBB.1.5 subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants (Part 1 of Study 2019nCoV-313) and (2) to determine if a single dose of NVX-CoV2601 in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induced noninferior antibody responses to the Omicron XBB.1.5 subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants (Part 1 of Study 2019nCoV-313). Both co-primary endpoints were achieved. 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.

Study 2019nCoV-314 – A phase 3, randomised, double-blind study to evaluate the safety and immunogenicity of Omicron subvariant (NVX-CoV2601) and bivalent (NVX-CoV2373 + NVX-CoV2601) SARS-CoV-2 rS vaccines in adolescents previously (≥ days) vaccinated with mRNA COVID-19 vaccines (400 participants exposed). The monovalent vaccine NVX-CoV2601 induced higher neutralising antibody responses following study vaccination compared to the neutralising antibody responses induced by the bivalent vaccine. Both vaccines were well tolerated with an acceptable safety profile. The frequency of solicited local injection site AEs and solicited systemic AEs of any grade was higher in the NVX-CoV2601 group than in the bivalent vaccine group.

Ongoing clinical trials

The MAH states that during the reporting interval, no interim analyses were planned or conducted for any of the ongoing clinical trials.

Study 2019nCoV-205 is an ongoing phase 2/3 randomised, 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. According to PSUR Appendix 7 (Table 35, p. 492), 902 participants have been exposed (planned enrolment: 990).

Study 2019nCoV-315 is a phase 3, open-label, single arm study to evaluate the safety and immunogenicity of a single dose of a JN.1 subvariant SARS-CoV-2 rS protein nanoparticle vaccine adjuvanted with Matrix-M (NVX-CoV2705) in previously vaccinated adults. According to PSUR Appendix 7 (Table 35, p. 493), 60 participants have been exposed (planned enrolment: 60).

Study 2019nCoV-415 is a prospective interventional study conducted at the University of Utah Health to assess the impact of reactogenicity among healthcare workers and first responders receiving

an updated 2024-25 Novavax COVID-19 vaccine (NVX-CoV2705) as compared with those receiving a 2024-25 Pfizer-BioNTech mRNA COVID-19 vaccine in a real-world setting in the US. According to PSUR Appendix 7 (Table 35, p. 494), 220 participants have been exposed to the Nuvaxovid vaccine (planned enrolment: 660).

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. According to PSUR Appendix 7 (Table 35, p. 495), 3,640 participants have been exposed (planned enrolment: 3,600; 1,200 in each age cohort).

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, Nuvaxovid XBB.1.5 or Nuvaxovid JN.1 were ongoing during the reporting interval.

New safety data related to fixed combination therapies

During the reporting interval, there was one ongoing company-sponsored phase 3 clinical trial, 2019nCoV-CIC-E-301, investigating the CIC vaccine comprising the JN.1-variant adapted COVID-19 vaccine (NVX-CoV-2705) co-formulated with the trivalent nanoparticle influenza hemagglutinin vaccine (tNIV) with Matrix-M adjuvant. There were no significant safety findings from the study as of the DLP.

Non-interventional studies

During the reporting interval, three company-sponsored post-authorisation safety studies (PASS) and three company-sponsored post-authorisation efficacy studies (PAES) were ongoing. No company-sponsored non-interventional studies were completed during the reporting interval. There was also one collaborative research PAES (BEEHIVE) and one collaborative surveillance study (2019nCoV-413) that were ongoing during the reporting interval. According to the MAH, 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 three ongoing and one completed investigator-initiated studies. The MAH states that no significant safety findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported.

Medication errors

Nuvaxovid. Using its pre-specified search strategy, the MAH retrieved one follow-up ICSR for the reporting interval. A cumulative total of 268 ICSRs were retrieved 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).

Nuvaxovid XBB.1.5. The MAH retrieved five initial and two follow-up ICSRs for the reporting interval. A cumulative total of 88 ICSRs were retrieved which contained 128 non-serious AEs. The most frequently reported PTs (n ≥ 10) were Expired product administered (n = 39), Product storage error (n = 38), and Product administration error (n = 28).

Nuvaxovid JN.1. The MAH retrieved 62 initial ICSRs for the reporting interval and cumulatively which contained 70 non-serious AEs. The most frequently reported PTs (n ≥ 5) were Expired product administered (n = 33), Extra dose administered (n = 7), Incorrect dose administered (n = 6) and Product preparation error (n = 5).

One observation of disproportionate reporting related to the PT 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.

Non-clinical data

During the reporting interval, there were four completed and 19 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 retrieved a total of 85 publications of which five presented new or significant findings on safety (n = 4) or safety and immunogenicity (n = 1). The MAH's review did not identify any new safety findings that impact the overall benefit-risk balance of Nuvaxovid vaccines. Six publications presented new or significant findings regarding efficacy (n = 1), effectiveness (n = 4), or efficacy and immunogenicity (n = 1).

Other periodic reports

The MAH lists three summary safety reports, with reporting intervals between 01 June 2024 and 31 October 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:

Two parts of a 4-part clinical trial, one part of a 2-part clinical trial and three other clinical trials were completed. The data provided does not reveal any new aspects that would change the conclusions of previous assessments. In addition, the MAH refers to four ongoing company-sponsored clinical trials, and PSUR Appendix 7 lists one completed (Table 37, p. 500) and three ongoing (Table 36, pp. 499-500) investigator initiated studies. No new safety findings were reported from three MAH-sponsored non-interventional PASS.

In ICSRs reporting medication error events, the most frequently recorded PT was Expired product administered (Nuvaxovid, n = 51; Nuvaxovid XBB.1.5, n = 39; Nuvaxovid JN.1, n = 33). The MAH reviewed these ICSRs and did not detect any trend beyond this isolated event of disproportionate reporting. Therefore, no signal requiring validation was generated.

Overall, the information presented by the MAH does not change the known safety profile of Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

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 10: Summary of safety concerns at the beginning of the reporting interval (RMP version 5.1, dated 14 June 2024; PSUR p. 171)

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

During the reporting period, the EU RMP was updated to version 6.1, dated 31 October 2024, to support the prefilled syringe presentation of the JN.1 variant-adapted vaccine. There were no changes to the list of safety concerns.

2.2. Signal evaluation

The MAH notes that no new signals were validated during the reporting interval.

Rapporteur assessment comment:

No new signal was generated during the reporting interval; no signal was ongoing and no signal was closed. PSUR Appendix 6 (Table 33, pp. 479-486) lists all safety signals evaluated so far. The signals of anaphylaxis, myopericarditis/myocarditis/pericarditis and paraesthesia had been confirmed and

resulted in updates of the CCDS. The signals of chest pain/chest discomfort, dizziness, encephalitis/ encephalomyelitis, menstrual disorders, tachycardia and other rhythm disorders, acute coronary syndrome associated with hypersensitivity, syncope, diarrhoea, dyspnoea, tinnitus, sensorineural hearing loss, oculomotor cranial nerve disorders, migraine and tachycardia had been refuted and closed.

2.3. Evaluation of risks and safety topics under monitoring

The MAH monitors the following **adverse events of special interest** (AESIs): Acute disseminated encephalomyelitis, acute kidney injury, acute liver injury, anaphylaxis, autoimmune hepatitis, autoimmune thyroiditis, Bell's palsy, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis/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.

Observed to expected (O/E) analyses are performed for all Novavax COVID-19 vaccines combined and individually for the variant adapted formulations (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1). Numerator data are derived from AESI search strategies. Denominator data are derived from actual and estimated exposure for all formulations combined and individually. 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, with the exception of anaphylaxis for which O/E analysis 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. Time-to-onset (TTO) of an AESI is calculated at the individual case level. Risk windows are applied according to published recommendations, and in instances where 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. Based on previous health authority requests, sensitivity analyses on specific risk windows are also conducted for some AESIs.

Cumulatively up to the DLP of 19 December 2024, no ICSRs were retrieved for the following nine AESIs for any Nuvaxovid formulation: Acute disseminated encephalomyelitis, foetal growth restriction, gestational diabetes, Kawasaki's disease, maternal death, microcephaly, narcolepsy, neonatal death, and stillbirth. In addition, for Nuvaxovid, no ICSRs reported the AESIs major congenital anomalies and oculomotor cranial nerve disorder. For Nuvaxovid XBB.1.5, an additional 17 AESIs have no associated ICSRs: Acute kidney injury, acute liver injury, anaphylaxis, autoimmune hepatitis, autoimmune thyroiditis, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis/ encephalomyelitis, Guillain-Barré syndrome, multiple sclerosis, multisystem inflammatory syndrome in children, myasthenia gravis, myocardial infarction, optic neuritis, thrombocytopenia, thrombosis with thrombocytopenia syndrome, and vaccine-associated enhanced disease. For Nuvaxovid JN.1, in addition to the nine AESIs for which no ICSRs have been reported for all Nuvaxovid COVID-19 vaccines, an additional 26 AESIs have no associated ICSRs: Acute kidney injury, acute liver injury,

autoimmune hepatitis, autoimmune thyroiditis, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis/encephalomyelitis, fibromyalgia, Guillain-Barré syndrome, major congenital anomalies, multiple sclerosis, multisystem inflammatory syndrome in children, myasthenia gravis, oculomotor cranial nerve disorders, optic neuritis, postural orthostatic tachycardia syndrome, preeclampsia, preterm birth, rheumatoid arthritis, spontaneous abortion, sudden death, thrombocytopenia, thrombosis with thrombocytopenia syndrome, transverse myelitis, vaccine associated enhanced disease, and venous thromboembolism.

During the reporting interval, no new AESI signals were validated and no new AESI crossed the threshold for statistical significance for the overall estimate. No significant changes in O/E were detected for any AESI.

Table 11: Number of ICSRs retrieved for AESIs monitored by the MAH and for which cases have been reported (PSUR section 15.2, pp. 95-156)

Number of ICSRs	**Nuvaxovid**		**Nuvaxovid XBB.1.5**		**Nuvaxovid JN.1**	
	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
Acute kidney injury	0	3	0	0	0	0
Acute liver injury	0	5	0	0	0	0
Anaphylaxis	3	75	0	0	2	2
Autoimmune hepatitis	0	2	0	0	0	0
Autoimmune thyroiditis	0	3	0	0	0	0
Bell's palsy	0	24	0	2	1	1
Cerebral venous sinus thrombosis	0	1	0	0	0	0
Chronic fatigue syndrome	0	3	0	0	0	0
Encephalitis and encephalomyelitis	0	5	0	0	0	0
Fibromyalgia	1	5	0	1	0	0
Generalised convulsions	0	13	2	4	2	2
Guillain-Barré syndrome	2	10	0	0	0	0
Haemorrhagic stroke	0	11	1	1	1	1
Ischaemic stroke	0	17	2	4	1	1
Major congenital anomalies	0	0	1	1	0	0
Multiple sclerosis	0	3	0	0	0	0
Multisystem inflammatory syndrome in children	0	1 (adult)	0	0	0	0
Myasthenia gravis	0	1	0	0	0	0
Myocardial infarction	0	16	0	0	5	5
Myocarditis	0	31	0	2	1	1
Pericarditis	0	57	1	4	2	2
Myocarditis and pericarditis	0	89	1	7	3	3
Oculomotor cranial nerve disorders	0	0	0	1	0	0
Optic neuritis	0	1	0	0	0	0
Postural orthostatic tachycardia syndrome	2	6	0	1	0	0
Preeclampsia	0	2	0	1	0	0
Preterm birth	0	2 (linked – maternal and neonate)	0	2 (linked – maternal and neonate)	0	0
Rheumatoid arthritis	0	8	0	1	0	0

Spontaneous abortion	0	4	0	1	0	0
Sudden death	0	1	0	1	0	0
Thrombocytopenia	0	9	0	0	0	0
Thrombosis with thrombocytopenia syndrome	0	1	0	0	0	0
Transverse myelitis	0	1	0	1	0	0
Vaccine associated enhanced disease	0	7	0	0	0	0
Venous thromboembolism	3	25	1	3	0	0

Further, the MAH queried its global vaccine safety database for the following **additional safety topics for monitoring** up to 19 December 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.

The MAH did not identify any new safety signal. 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 12: Number of ICSRs retrieved for additional safety topics monitored by the MAH (PSUR section 15.3, pp. 157-170)

Number of ICSRs	**Nuvaxovid**		**Nuvaxovid XBB.1.5**		**Nuvaxovid JN.1**	
	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
Death, all cause	1	35	1	8	5	5
Cholecystitis	0	9	0	1	1	1
Diarrhoea	2	139	2	9	7	7
Herpes zoster	0	40	1	2	1	1
Inflammatory eye disorders	2	66	0	4	5	5
Menstrual disorders	0	138	0	0	1	1
Paraesthesia	5	419	2	21	13	13
Reactogenicity profile – second dose and boosters (based on impurity levels)	28	321	3	12	9	9
Safety concerns in elderly	10	734	18	112	121	121
Off-label paediatric use (< 12 years)	0	12	1	4	2	2
Tinnitus	0	87	1	10	3	3
Vaccine anxiety-related reactions	3	60	1	4	2	2
Vaccination failures*/ lack of efficacy	2	22	4	10	2	2

*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 added acute kidney injury and acute liver injury to its list of prospectively monitored AESIs. This is endorsed. Compared to previous analyses, no new aspects emerged from the MAH's O/E calculations. Taking into consideration the MAH's review of the risks, no further action is considered

warranted at this stage.

2.4. Characterisation of risks

For the characterisation of important identified/potential risks and missing information, the MAH refers to the EU RMP version 6.1, dated 31 October 2024, Part II, Module SVII.

New information on important identified risks

Myocarditis and/or pericarditis

Nuvaxovid: For the reporting interval, the MAH retrieved two initial and one follow-up ICSRs. Of a cumulative total of 138 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 29, p. 175) 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 three initial ICSRs. Of a cumulative total of 18 ICSRs, one met level 1-3 Brighton Collaboration case definitions for myocarditis and/or pericarditis.

Nuvaxovid JN.1: For the reporting interval and cumulatively, the MAH retrieved five ICSRs. Of these, three 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 five confirmed cases of myocarditis with Nuvaxovid (adjudicated against a modified algorithm based on the Brighton Collaboration case definition). Four of the five 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 or Nuvaxovid JN.1.

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

An ICSR was not retrieved for any of the vaccines for the reporting interval.

Update on missing information

Use in pregnancy and while breastfeeding

Nuvaxovid: As regards use in pregnancy, the MAH retrieved one initial ICSR for the reporting interval and 16 ICSRs cumulatively. Nuvaxovid XBB.1.5: As regards use in pregnancy, the MAH retrieved no ICSR for the reporting interval, and a cumulative total of 16 ICSRs. Nuvaxovid JN.1: As regards use in pregnancy, the MAH retrieved no ICSR for the reporting interval and cumulatively.

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: As regards foetal and neonate ICSRs, one follow-up 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 ICSR was retrieved for the reporting interval, and four ICSRs were retrieved cumulatively involving three foeti and one neonate. Nuvaxovid JN.1: No ICSR was retrieved either for the reporting interval or cumulatively. The MAH did not identify any safety signal.

Nuvaxovid: Concerning use while breastfeeding, no ICSR was retrieved for the reporting interval, and three ICSRs were retrieved cumulatively. Nuvaxovid XBB.1.5: No ICSR was retrieved either cumulatively or for the reporting interval. Nuvaxovid JN.1: One initial ICSR was retrieved for the reporting interval and cumulatively. According to the MAH, none of the reports of use during pregnancy and breastfeeding raised any safety concerns.

Use in immunocompromised patients

Nuvaxovid: The MAH retrieved two initial and two follow-up ICSRs for the reporting interval and 31 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved three initial and one follow-up ICSRs for the reporting interval and nine ICSRs cumulatively. Nuvaxovid JN.1: The MAH retrieved seven initial ICSRs for the reporting interval and 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 nine initial and 17 follow-up ICSRs for the reporting interval and 656 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved 13 initial and four follow-up ICSRs for the reporting interval and 144 ICSRs cumulatively. Nuvaxovid JN.1: The MAH retrieved 89 initial ICSRs for the reporting interval and 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 one initial and four follow-up ICSRs for the reporting interval and 214 ICSRs cumulatively. Nuvaxovid XBB.1.5: The MAH retrieved two initial and two follow-up ICSRs for the reporting interval and 56 ICSRs cumulatively. Nuvaxovid JN.1: The MAH retrieved 42 initial ICSRs for the reporting interval and 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 either for the reporting interval or cumulatively. Nuvaxovid JN.1: The MAH retrieved no ICSR either for the reporting interval or cumulatively. 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 PASS. There were three ongoing PASS 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 seven 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 seven 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 five/four cases of severe COVID-19 reported in the placebo recipients.

According to the MAH, 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.

On 08 October 2024, the European Commission granted marketing authorisation for Nuvaxovid JN.1 dispersion for injection COVID-19 vaccine (recombinant, adjuvanted), for use in individuals aged 12 and older for the prevention of COVID-19 in the EU. The effectiveness and safety of Nuvaxovid JN.1 is based on the totality of evidence from clinical trials, including efficacy and effectiveness data with the Novavax COVID-19 vaccine, adjuvanted (original monovalent) and immunogenicity data of the monovalent vaccine (Omicron BA.1) and monovalent vaccine (Omicron BA.5).

The MAH presents a subsection providing information that became available in the literature (6 publications) during the reporting interval of this PBRER, either on the efficacy/effectiveness (n = 5) or efficacy/effectiveness and immunogenicity of Nuvaxovid vaccines (n = 1).

Rapporteur assessment comment:

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

Note: As in the previous PSUR (procedure EMEA/H/C/PSUSA/00010972/202406), when presenting the results of study 2019nCoV-302, the MAH gives inconsistent numbers of severe COVID-19 cases in placebo recipients (five and four, PSUR p. 190). This might be clarified in the next report.

4. Benefit-risk balance

The data presented in this PSUR does not alter previous assessments of safety, efficacy or effectiveness. The PRAC rapporteur therefore concludes that the benefit-risk balance for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 remains unchanged in its authorised indications.

5. Rapporteur request for supplementary information

Not applicable.

6. <MAH responses to Request for supplementary information>

Rapporteur assessment comment:

7. < Comments from Member States >

Member states' comments:

PERIODIC BENEFIT-RISK EVALUATION REPORT

FOR

PRODUCT: NUVAXOVID/NUVAXOVID XBB.1.5/NUVAXOVID JN.1 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
	EU/1/21/1618/005 EU/1/21/1618/010	08-Oct-2024	
NUVAXOVID JN.1	EU/1/21/1618/007 EU/1/21/1618/009	08-Oct-2024	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-Jun-2024 to 19-Dec-2024

Date of Report: 13-Feb-2025

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

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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
APPROVED BY:	[redacted] EU QPPV Global Vaccine Safety	[redacted]
APPROVED BY:	[redacted] Vice President, Head of Medical Safety Global Vaccine Safety	
APPROVED BY:	[redacted] Vice President, Head of Safety Sciences and Surveillance Global Vaccine Safety	

EXECUTIVE SUMMARY

Introduction

This is the sixth Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™, summarising interval and cumulative safety data received by Novavax (NVX) for the reporting interval 20-Jun-2024 to 19-Dec-2024. This PBRER also includes exposure and safety data for Nuvaxovid™ XBB.1.5 and Nuvaxovid™ JN.1, which are Nuvaxovid updated vaccines for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron XBB.1.5 sub-variant and JN.1 sub-variant, respectively. As used in this report, the term "original vaccine" refers to Nuvaxovid, the term "XBB.1.5 vaccine" refers to Nuvaxovid XBB.1.5, the term "JN.1 vaccine" refers to Nuvaxovid JN.1 and the term "Novavax COVID-19 vaccines" refers to Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

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]), 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 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 Omicron JN.1, respectively. Currently 3 of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373), Nuvaxovid XBB.1.5 (NVX-CoV2601) and Nuvaxovid JN.1 (NVX-CoV2705). In this report, the trade names, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 as described above are used when referring to these vaccines in the post-authorisation/post-marketing setting. Novavax's study vaccine names, NVX-CoV2373 (or Prototype), NVX-CoV2601(XBB.1.5) and NVX-CoV2705 (JN.1), are used when referring to these vaccines in clinical trials. The table below describes the properties of Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 as mentioned in the EU Summary of Product Characteristics (SmPC).

Parameter	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Vaccine code	NVX-CoV2373	NVX-CoV2601	NVX-CoV2705
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5	SARS-CoV-2 Omicron variant lineage JN.1
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 vials [1] containing either 5 or 10 doses per vial	Single or Multi-dose vials Multi-dose vial containing 5 doses per vial	Single-dose vials [2]
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. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.	Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

[1] Nuvaxovid is also approved as prefilled syringes in South Korea.

[2] Nuvaxovid JN.1 is also approved as prefilled syringes (US and South Korea) and as multi-dose vials in other regions.

Worldwide Marketing Authorisation Status

Nuvaxovid:

Nuvaxovid received marketing authorisation or was 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 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 booster in individuals 12 years of age and older. In addition, the WHO granted authorisation for both Nuvaxovid and Covovax.

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 Taiwan.
- Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) (Nuvaxovid XBB.1.5) was withdrawn in the US, in parallel with authorization of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), (Nuvaxovid JN.1).

Nuvaxovid JN.1:

Nuvaxovid JN.1 received authorisation for emergency use or received marketing authorisation for individuals 12 years and older in multiple countries and the EU region. Alternative names for Nuvaxovid JN.1 include Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in the US.

During the reporting interval:

- Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) received emergency use authorisation in the US and South Korea.
- Nuvaxovid JN.1 received authorisation in Canada, EU, Japan, Singapore and the United Kingdom.

Actions Taken for Safety Reasons

None.

Changes to Reference Safety Information

The Company Core Data Sheet (CCDS) Version (v) 10.0, dated 30-May-2024 was in effect at the beginning and at the end of the reporting interval and is used as Reference Safety Information for this PBRER. No updates were made to the CCDS during the reporting interval.

Clinical Trial Exposure

Cumulatively, 49,962 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. An additional 1,422 participants were exposed to the prototype SARS-CoV-2 rS vaccine in 2 NVX sponsored clinical trials involving a COVID-19 influenza combination (CIC) vaccine. A total of 5,625 participants are engaged in blinded treatment arms of studies across the NVX sponsored SARS-CoV-2rS and CIC clinical development programs.

Post-Authorisation Exposure

Summary of Interval and Cumulative Administration of Novavax COVID-19 Vaccines

Timeframe	Nuvaxovid [2]	Nuvaxovid XBB.1.5 [2]	Nuvaxovid JN.1	Novavax COVID-19 Vaccines
Interval [1]	1,608	9,888	703,643	715,139
Cumulative	2,990,785	1,212,889	703,643	4,907,317

[1] Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source.

[2] Includes Novavax and Serum Institute of India Pvt Ltd. (SIIPL) products corresponding to the Novavax COVID-19 vaccines.

Overview of Signals: New, Ongoing, or Closed

No new signals were validated during the current reporting interval.

The signals of anaphylaxis, paraesthesia, myopericarditis, myocarditis and pericarditis have been previously confirmed and the CCDS 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, tinnitus 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 during the reporting interval.

Overall Benefit-Risk Evaluation

Based on the totality of the data across the SARS-CoV-2 rS clinical development program and post authorization setting, 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 lifecycle, the benefits of the Novavax COVID-19 vaccines outweigh known and potential risks 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-Dec-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
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AESI(s)	Adverse Event(s) of Special Interest
BALB/c	Albino, Laboratory-Bred Strain of the house Mouse, MHC Haplotype H2d
BEST	Biologics Effectiveness and Safety
BLA	Biologics License Application
BODIPY	Boron-Dipyrromethane
CBER	Centre For Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CI	Confidence Interval
CIC	COVID-19 Influenza Combination Nanoparticle Vaccine
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, Elisa Unit
EU/mL	ELISA Units per mL
EUA	Emergency Use Authorisation
EUL	Emergency Use Listing
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

Acronym	Abbreviation Definition
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
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
IL-2	Interleukin 2
IM	Intramuscular
IME	Important Medical Event
J-NDA	Japanese New Drug Application
KDCA	Korean Disease Control and Prevention Agency
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
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

Acronym	Abbreviation Definition
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PIMMC(s)	Potential Immune Mediated Medical Condition(s)
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
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
SCR	Seroconversion rate
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)
SSR	Summary Safety Report
TEAE(s)	Treatment Emergent Adverse Event(s)
TGA	Therapeutic Goods Administration
Th1	Type 1 T helper
TNFα	Tumor Necrosis Factor Alpha
TTO	Time to Onset
UK	United Kingdom
US	United States
v	Version
VE	Vaccine Efficacy
VOC	Variant of Concern

Acronym	Abbreviation Definition
VOI	Variant of Interest
vs	Versus
WHO	World Health Organisation
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the sixth Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™, summarising interval and cumulative safety data received by Novavax (NVX) for the reporting interval 20-Jun-2024 to 19-Dec-2024. This PBRER includes exposure and safety data for Nuvaxovid™, Nuvaxovid™ XBB.1.5 and Nuvaxovid™ JN.1. As used in this report, the term "original vaccine" refers to Nuvaxovid, the term "XBB.1.5 vaccine" refers to Nuvaxovid XBB.1.5, the term "JN.1 vaccine" refers to Nuvaxovid™ JN.1 and the term "Novavax COVID-19 vaccines" refers to Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

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]), and the Consideration on core requirements for RMPs of COVID-19 vaccines - core RMP19 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 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 the original SARS-CoV-2 Wuhan strain, and variants Omicron BA.1, Omicron BA.5, Omicron XBB.1.5, or Omicron JN.1, respectively. Currently 3 of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373), Nuvaxovid XBB.1.5 (NVX-CoV2601) and Nuvaxovid JN.1 (NVX-CoV2705). In this report, the trade names, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 as described above, are used when referring to these vaccines in the post-authorisation/post-marketing setting, while Novavax's study vaccine names, NVX-CoV2373 (or Prototype), NVX-CoV2601 (XBB.1.5) and NVX-CoV2705 (JN.1), are used when referring to these vaccines in clinical trials. Table 1 below describes the properties of Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 as mentioned in the EU Summary of Product Characteristics (SmPC).

During the reporting interval, 2 parts of a 4-part clinical trial (2019nCoV-301 Adolescent Main and Adolescent Booster), one part of a 2-part clinical trial (2019nCoV-311 Part 2) and 3 other clinical trials (2019nCoV-312, 2019nCoV-313 [Parts 1 and 2] and 2019nCoV-314) were completed. As of the data lock point (DLP) (19-Dec-2024), 4 NVX-sponsored clinical

trials (2019nCoV-205, 2019nCoV-315, 2019nCoV-415 and 2019nCoV-503) 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 and Nuvaxovid JN.1

Parameters	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Vaccine code	NVX-CoV2373	NVX-CoV2601	NVX-CoV2705
Strain	SARS-CoV-2 Wuhan-Hu 1 strain (Original)	SARS-CoV-2 Omicron variant lineage XBB.1.5	SARS-CoV-2 Omicron variant lineage JN.1
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 vials containing either 5 or 10 doses per vial [1]	Single or Multidose vials Multi-Dose vial containing 5 doses per vial	Single-dose vials [2]
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. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.	Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status. For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least 3 months after the most recent dose of a COVID-19 vaccine. Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations

[1] Nuvaxovid is also approved as prefilled syringes in South Korea.

[2] Nuvaxovid JN.1 is also approved as prefilled syringes (US and South Korea) and as multi-dose vials in other regions.

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 and in the EU SmPC in Appendix 2.

Additional safety topics and reporting requirements for countries/regions are presented as follows: Australia in Appendix 14, Canada in Appendix 15, the EU in Appendix 16, the United Kingdom (UK) in Appendix 17 and the United States (US) in Appendix 18.

2 WORLDWIDE MARKETING AUTHORISATION STATUS

Nuvaxovid:

Nuvaxovid received marketing authorisation or was 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 granted authorisation for both Nuvaxovid and Covovax. Refer to Appendix 3, Table 30 for the Worldwide Marketing Authorisation (WWMA) Status.

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 Taiwan.
- Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) (Nuvaxovid XBB.1.5) was withdrawn in the US, in parallel with authorization of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) (Nuvaxovid JN.1).

Additional details regarding the WWMA status are provided in Appendix 3 Table 31.

Nuvaxovid JN.1:

Nuvaxovid JN.1 received authorisation for emergency use or received marketing authorisation for individuals 12 years and older in multiple countries and the EU region. Alternative names for Nuvaxovid JN.1 include Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) in US.

During the reporting interval:

- Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) received emergency use authorisation (EUA) in US and South Korea.
- Nuvaxovid JN.1 received authorisation in Canada, EU, Japan, Singapore and UK.

Additional details regarding the WWMA status are provided in Appendix 3 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 and end of the reporting interval was the Company Core Data Sheet (CCDS), Version (v) 10.0, effective date 30-May-2024 (Appendix 1).

4.1 Safety Variations

During the reporting interval, NVX submitted the following safety variation and received approval:

- Removal of tinnitus from the Health Canada Product Monograph

4.2 Summary of Changes to CCDS

No updates were made to the CCDS during the reporting interval.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative Subject Exposure in Clinical Trials

Overall cumulative exposure in clinical trials is described in Table 2. Stratification by age, sex and race is provided in Table 3, Table 4 and Table 5, respectively.

The NVX COVID-19 vaccines in clinical development are:

Monovalent vaccines

- Prototype (NVX-CoV2373)
- BA.1 (NVX-CoV2515)
- BA.5 (NVX-CoV2540)
- XBB.1.5 (NVX-CoV2601)
- JN.1 (NVX-CoV2705)

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 Influenza Combination (CIC) nanoparticle vaccines:

- Prototype (NVX-CoV2373) + quadrivalent nanoparticle influenza vaccine
- JN.1 (NVX-CoV2705) + trivalent nanoparticle influenza vaccine

Table 2: Cumulative Participant Exposure by Clinical Trial and Study Treatment

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA.1	BA.5	CIC [5]	Prototype	Prototype +BA.1	Prototype +BA.5	XBB.1.5	Prototype +XBB.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-101 Part 1	23	–	–	–	108	–	–	–	–	–	–	108
2019nCoV-101 Part 2	254	–	–	–	1,029	–	–	–	–	–	–	1,029
2019nCoV-205	–	–	–	–	91	–	–	811	–	–	–	902 [1]
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 Part 1	–	–	–	–	–	–	–	332	–	–	–	332
2019nCoV-313 Part 2	–	–	–	–	–	–	–	338	–	–	–	338
2019nCoV-314	–	–	–	–	–	–	–	190	210	–	–	400
2019nCoV-315	–	–	–	–	–	–	–	–	–	60	–	60
2019nCoV-501	304	–	–	–	4,104	–	–	–	–	–	–	4,104

Table 2: Cumulative Participant Exposure by Clinical Trial and Study Treatment

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	**BA.1**	**BA.5**	**CIC [5]**	**Prototype**	**Prototype +BA.1**	**Prototype +BA.5**	**XBB.1.5**	**Prototype +XBB.1.5**	**JN.1**	**Blinded Treatment**	**Total (Excl. Placebo)**
2019nCoV-503	–	–	–	–	–	–	–	–	–	–	3,640	3,640 [2]
2019nCoV-505	–	–	–	–	383	–	–	–	–	–	–	383
2019nCoV-ICC-E-101 [5]	–	–	–	558	78	–	–	–	–	–	–	636
2019nCoV-CIC-E-201 [5]	–	–	–	864	315	–	–	–	–	–	–	1,179
CIC-E-301 [5]	–	–	–	–	–	–	–	–	–	–	1,985	1,985
Total	**8,460**	**347**	**297**	**1,422**	**46,776**	**269**	**259**	**1,671**	**210**	**60**	**5,625**	**56,936 [3,4]**

[1] 91 participants who took mRNA were excluded from the 2019nCoV-205 study total.

[2] For Study 503, some participants were identified for cross-enrolment in different sites. For example, the same participant could have three different subject IDs when the participant enrolled in the study from three different sites. In the current statistical programming, unique participants were counted instead of counting all subject IDs. Therefore, the number of participants in Study 503 in the current tables is less than the PBRER No.05 table which counted all subject IDs.

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

[4] Exposure from participants in the 2019nCoV-415 study (n=220) was reported separately and therefore exposure from that study was excluded from this table.

[5] The CIC vaccine in 2019nCoV-ICC-E-101 and 2019nCoV-CIC-E-201 comprised prototype (NVX-CoV2373) + quadrivalent nanoparticle influenza vaccine and Matrix-M adjuvant. The CIC vaccine in CIC-E-301 comprised NVX-CoV2705+trivalent nanoparticle influenza vaccine and Matrix-M adjuvant.

Table 3: 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**	**Prototype +XBB.1.5**	**JN.1**	**Blinded**	**Total (Excl Placebo)**
6 – < 24 months	–	–	–	–	–	–	–	–	–	–	1,164	1,164
2 – < 6 years	–	–	–	–	–	–	–	–	–	–	1,216	1,216
6 – < 12 years	–	–	–	–	–	–	–	–	–	–	1,260	1,260
12 – < 18 years	75	–	–	–	2,157	–	–	190	210	–	–	2,557
18 – 34 years	1,437	135	92	–	12,089	97	69	186	–	3	–	12,671
35 – 50 years	1,938	143	143	52	13,930	113	122	225	–	15	–	14,743
51 – 65 years	2,879	69	54	956	13,142	59	60	565	–	22	110	15,037
> 65 years	2,131	–	8	414	5,458	–	8	505	–	20	1,875	8,288
Total	**8,460**	**347**	**297**	**1,422**	**46,776**	**269**	**259**	**1,671**	**210**	**60**	**5,625**	**56,936** [1,2]

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

[2] Exposure from participants in the 2019nCoV-415 study (n=220) was reported separately, and therefore exposure from that study was excluded from this table.

Table 4: 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**	**Prototype +XBB.1.5**	**JN.1**	**Blinded**	**Total (Excl Placebo)**
Male	4,343	155	133	586	24,235	118	120	698	103	22	2,940	29,110
Female	4,117	192	164	836	22,541	151	139	973	107	38	2,685	27,826
Total	**8,460**	**347**	**297**	**1,422**	**46,776**	**269**	**259**	**1,671**	**210**	**60**	**5,625**	**56,936** [1,2]

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

[2] Exposure from participants in the 2019nCoV-415 study (n=220) was reported separately, and therefore exposure from that study was excluded from this table.

Table 5: 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**	**Prototype +XBB.1.5**	**JN.1**	**Blinded**	**Total (Excl Placebo)**
Aboriginal Australian	–	–	–	1	3	–	–	–	–	–	5	9
African	–	–	–	–	–	–	–	–	–	–	2	2
American Indian or Alaska Native	199	–	–	2	1,847	–	–	15	–	1	132	1,997
Asian	314	48	39	43	1,769	39	26	27	2	1	915	2,909
Black or African American	598	1	16	–	7,985	–	–	370	44	12	733	9,161
Maori	–	–	–	14	2	–	–	–	–	–	44	60
Native Hawaiian or Other Pacific Islander	5	3	2	5	81	1	1	5	1	–	34	133
Southern African Coloured	–	–	–	–	–	–	–	–	–	–	1	1
White or Caucasian	7,224	280	220	1,314	33,886	220	215	1,202	149	45	2,518	40,049
Other	12	10	14	17	149	8	14	8	2	–	1,161	1,383
Multiple	63	5	6	15	728	1	1	23	10	1	20	810
Missing or Not Reported	45	–	–	11	326	–	2	17	1	–	60	417
Unknown	–	–	–	–	–	–	–	4	1	–	–	5
Total	**8,460**	**347**	**297**	**1,422**	**46,776**	**269**	**259**	**1,671**	**210**	**60**	**5,625**	**56,936** [1,2]

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

[2] Exposure from participants in the 2019nCoV-415 study (n=220) was reported separately, and therefore exposure from that study was excluded from this table.

Exposure from participants in the 2019nCoV-415 study (n=220) was reported separately, and therefore exposure from that study was excluded from the above tables. Demographic details of these participants are not available.

5.2 Cumulative and Interval Exposure in the Post-Authorisation Setting

Cumulative and interval post authorisation exposure data for Novavax Covid-19 vaccines are presented in Table 6 and stratified by country/region in Table 7.

Distribution data (Table 42 and Table 43) and the sources for administration and distribution data are summarised in Appendix 10. Distribution data have been adjusted for returned doses.

Novavax does not have access to data regarding post-authorisation use in special populations. At this time, post-authorization safety studies with Novavax COVID-19 vaccines are not sufficiently powered to provide any information on exposure in special populations. Safety data in special populations, based on spontaneous reports, are summarized in the appropriate sections (Sections 16.3.5.1 Use in Pregnancy and While Breastfeeding; 16.3.5.2 Use in Immunocompromised Patients; 16.3.5.3 Use in Frail Patients with Comorbidities; 16.3.5.4 Use in Patients with Autoimmune or Inflammatory Disorders; 15.3.9 Review of Safety Concerns in Elderly and Off-label Pediatric Use).

Table 6: Summary of Interval and Cumulative Administration Data of Novavax COVID-19 Vaccines

Timeframe	Nuvaxovid [2]	Nuvaxovid XBB.1.5 [2]	Nuvaxovid JN.1	Novavax COVID-19 Vaccines
Interval [1]	1,608	9,888	703,643	715,139
Cumulative	2,990,785	1,212,889	703,643	4,907,317

[1] Exposure estimates are subject to available vaccine administration data with cut off dates determined by the exposure source as indicated in Table 41.

[2] Includes Novavax and SIIPL products corresponding to the Novavax COVID-19 vaccines.

Table 7: Interval and Cumulative 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	Nuvaxovid JN.1
Interval (20-Jun-2024 to 19-Dec-2024)			
Australia (Biocelect Pty Ltd.) [1]	NA	0	NA
Canada [1]	1,608	5,081	NA
EU [1]	0	0	NA
Germany [1]	NA	0	NA
India [2]	0	0	NA
Indonesia [2]	NA	0	NA
Israel (Medicalix/Freyr) [1]	NA	0	NA
Japan (Takeda) [1]	NA	0	NA

Table 7: Interval and Cumulative 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	Nuvaxovid JN.1
Interval (20-Jun-2024 to 19-Dec-2024)			
New Zealand (Biocelect New Zealand Ltd) [1]	NA	0	NA
Singapore (PharmEng Technology Pte Ltd) [1]	NA	0	NA
South Korea (SK Bioscience) [1]	0	477	65,262
Switzerland [1]	NA	0	NA
Taiwan [1]	NA	0	NA
Thailand [2]	NA	0	NA
UK [1]	0	0	NA
US [1]	0	4,330	638,381
Novavax Total (incl Takeda and SK Bio)	**1,608**	**9,888**	**703,643**
SIIPL Total	**0**	**Not Applicable**	**Not Applicable**
Interval Total	**1,608**	**9,888**	**703,643**
Cumulative (20-Dec-2021 to 19-Dec-2024)			
Australia (Biocelect Pty Ltd.) [1]	273,670	NA	NA
Canada [1]	38,951	5,529	NA
EU [1]	355,807	683,899	NA
Germany [1]	160,154	NA	NA
India [2]	54,933	NA	NA
Indonesia [2]	NA	NA	NA
Israel (Medicalix/Freyr) [1]	43	NA	NA
Japan (Takeda) [1]	349,779	NA	NA
New Zealand (Biocelect New Zealand Ltd) [1]	7,867	NA	NA
Singapore (PharmEng Technology Ltd) [1]	40,873	NA	NA
South Korea (SK Bioscience) [1]	974,574	12,788	65,262
Switzerland [1]	3,073	NA	NA
Taiwan [1]	640,584	262,343	NA
Thailand [2]	NA	NA	NA
UK [1]	1,282	NA	NA
US [1]	89,195	248,330	638,381
Novavax Total (incl Takeda and SK Bio)	**2,935,852**	**1,212,889**	**703,643**
SIIPL Total	**54,933**	**Not Applicable**	**Not Applicable**
Cumulative Total	**2,990,785**	**1,212,889**	**703,643**

[1] Novavax as MAH.

[2] SIIPL as MAH.

Abbreviations: NA – Not Available.

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), v27.1 was used for the coding of SAEs and ADRs.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 4 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, NVX-CoV2705 from the development international birth date (DIBD) (23-Apr-2020) to the DLP (19-Dec-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-315, 2019nCOV-415, 2019nCOV-501, 2019nCOV-503 and 2019nCOV-505.

Clinical study data are extracted from the NVX global safety database and may contain unblinded information. Data are presented by MedDRA System Organ 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.

NOTE: In response to the Pharmacovigilance Risk Assessment Committee (PRAC) assessor comment received in PBRER No.05, NVX has provided a summary tabulation generated from the safety database by individual vaccines as available in the safety database configuration (Appendix 4A). Due to the style of configuration of the individual vaccines in the safety database, the summary tabulation generated from the safety database was consolidated manually to combine the vaccines within the respective groups (Appendix 4B). For completeness, both the system generated report (Appendix 4A) and the manually-consolidated report (Appendix 4B) are provided in Appendix 4.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

Appendix 5 presents interval and cumulative counts of serious and non-serious adverse reactions for all spontaneous, regulatory authority, and literature sources, and serious adverse

reactions from non-interventional studies. All Individual Case Safety Reports (ICSRs) data reflect the version valid at the time of the DLP.

Appendix 5A: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Authorisation Data Sources for Nuvaxovid

Appendix 5B: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Authorisation Data Sources for Nuvaxovid XBB.1.5

Appendix 5C: Cumulative and Interval Summary Tabulation of Serious and Non-Serious Adverse Reactions from Post-Authorisation Data Sources for Nuvaxovid JN.1

6.3.1 Overview of Interval and Cumulative Post-Authorisation Data for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1

Table 8 summarises all post-authorisation ICSRs in the database that were approved during the reporting interval and cumulatively.

Note: Appendix 5 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 (Section 6.3.1) include all adverse events (AEs) (irrespective of causality); therefore counts in this section may not align with the counts presented in Appendix 5.

Table 8: Overview of Interval and Cumulative ICSRs and AEs for Novavax COVID-19 Vaccines

Parameters		Nuvaxovid (Cumulative Administered Doses = 2,990,785)		Nuvaxovid XBB.1.5 (Cumulative Administered Doses = 1,212,889)		Nuvaxovid JN.1 (Cumulative Administered Doses = 703,643)	
		Interval [1]	Cumulative	Interval [1]	Cumulative	Interval [1]	Cumulative
Number of ICSRs		98 (50 initial, 48 follow-up)	5,198	123 (111 initial, 12 follow-up)	613	361 (initial)	361
Serious ICSRs (including fatal)		30	1,028	22	86	56	56
Non-Serious ICSRs		68	4,170	101	527	305	305
Fatal ICSRs		1 (initial)	35	1 (follow-up)	8	5 (initial)	5
Number of AEs		352	18,567	303	2,147	1003	1003
Serious AEs		116	2,923	48	211	141	141
Non-serious AEs		236	15,644	255	1,936	862	862
Number of ICSRs classified by age group	Foetus [2]	1	1	1	3	–	–
	Neonate [2]	–	3	–	1	–	–
	Infant [3]	–	1	1	1	–	–
	Child	–	8	–	2	2	2
	Adolescent	7	66	–	5	13	13
	Adult	56	3,759	29	187	143	143
	Elderly	10	734	18	112	121	121
	Unknown	24	626	74	302	82	82

[1] Includes both initial and follow-up ICSRs.

[2] Secondary exposure during pregnancy.

[3] Off-label use.

The overall Nuvaxovid adverse event reporting rate has decreased over time and with the introduction of variant-adapted vaccines from 0.17 to 0.05 ICSR per 100 doses.

A total of 5,198 ICSRs were reported with Nuvaxovid corresponding to a reporting rate of 0.17 ICSR per 100 vaccinations (5,198/2,990,785 doses administered). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n=5327 AEs; PT Fatigue n=704), Nervous system disorders (n=3113; PT Headache n=1067), Musculoskeletal and connective tissue disorders (n=2028; PT Myalgia n=712), Gastrointestinal disorders (n=1213; PT Nausea n=472), and Skin and subcutaneous tissue disorders (n=1065; PT Rash n=292).

A total of 613 ICSRs were reported with Nuvaxovid XBB.1.5, corresponding to a reporting rate of 0.05 ICSR per 100 vaccinations (613/1,212,889 doses administered). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n=808 AEs, PT Fatigue n=123), Musculoskeletal and connective tissue disorders (n=274; PT Myalgia n=93), Nervous system disorders (n=257; PT Headache n=117), Injury, poisoning and procedural complications (n=173; PT Expired product administered n=39), and Gastrointestinal disorders (n=143; PT Nausea n=62).

A total of 361 ICSRs were reported with Nuvaxovid JN.1, corresponding to a reporting rate of 0.05 ICSRs per 100 vaccinations (361/703,643 doses administered). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n=315 AEs; PT Pyrexia=36), Nervous system disorders (n=154; PT Headache n=39), Musculoskeletal and connective tissue disorders (n=112; PT Pain in extremity n=38), Injury, poisoning and procedural complications (n=89; PT Expired product administered n=33), and Gastrointestinal disorders (n=64; PT Nausea n=23).

6.3.2 Aggregate Adverse Event Data from South Korea

Nuvaxovid was licensed in South Korea on 12-Jan-2022 by SK Bioscience Co., Ltd. The Ministry of Food and Drug Safety in the Republic of Korea further granted EUA to Novavax COVID-19 Vaccine 2023-2024 formula on 29-Nov-2023, and to Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) on 30-Sep-2024.

The Korean Disease Control and Prevention Agency (KDCA) publishes the COVID-19 Vaccine Safety Report, which includes cumulative safety data for Nuvaxovid. This section summarises cumulative safety data from the COVID-19 Vaccine Safety Report [KDCA 2024] (Week 191) covering the period from 26-Feb-2021 to 27-Oct-2024. As per the report, a total of 974,574 Nuvaxovid doses were administered with a corresponding total of 1,298 ICSRs reported; a total of 12,312 doses of Novavax COVID-19 Vaccine 2023-2024 formula were administered with a corresponding total of 4 ICSRs reported; and a total of 65,262 doses of Novavax COVID-19 Vaccine Adjuvanted (2024-2025 formula) were administered with no ICSRs reported.

Note: Aggregate data from the KDCA report includes safety information up to 27-Oct-2024. Because individual ICSR data are received from the Korean Adverse Event Reporting System in 6-month intervals, the AE counts in this section may not be reflected in other sections of this document. Table 9 and Table 10 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 9: 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) [1]	Number of Cases		
	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Myalgia	278	1	0
Headache	260	0	0
Dizziness	180	0	0
Chest pain	172	0	0
Allergic reaction	171	2	0
Vaccination Site Pain, Rash, Swelling within 3 days of vaccination	138	0	0
Queasy	118	0	0
Dyspnoea (Breathlessness)	102	0	0
Itching	90	0	0
Chills	88	0	0
Pyrexia	80	1	0
Vomiting	54	0	0
Cellulitis (Inflammation at the injection site, not an abscess)	39	0	0
Abdominal pain	38	0	0
Diarrhoea	32	0	0
Lymph gland infection	32	0	0
Abnormal uterine bleeding	29	0	0
Arthritis	29	0	0
Severe local adverse reactions	16	0	0
Acute paralysis	14	0	0
Anaphylactoid reaction	8	0	0
Acute Cardiovascular injuries	7	1	0
Vaccine associated enhanced disease	7	0	0
Anaphylactic reaction	4	0	0

Table 9: 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) [1]	Number of Cases		
	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Vaccination site abscess	4	0	0
Alopecia [2]	3	0	0
Encephalopathy or Encephalitis	3	0	0
Guillain-Barre syndrome	3	0	0
Thrombosis	3	0	0
Visual acuity reduced [2]	3	0	0
Acute aseptic arthritis	1	0	0
Acute liver injury	1	0	0
Acute renal injury	1	0	0
Anosmia	1	0	0
Convulsion (Convulsion/Seizure)	1	0	0
Multiple Organ inflammatory syndrome	1	0	0

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

[2] 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.

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 10. No new fatal events have been reported, and data remains unchanged from the previous PBRER.

Table 10: Characteristics of South Korean cases with fatal outcomes

Characteristics	Nuvaxovid Case Count
Total	**13**
Sex	
Male	7
Female	6
Age range in years	
10 – 19	–
20 – 29	1
30 – 39	–
40 – 49	–
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	–
2 days	1
≥ 3 days	11
Autopsy	
Done	–
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 191 KDCA report.

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

This section summarises clinically important 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-Jun-2024 to 19-Dec-2024). Table 11 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-Dec-2024) for this PBRER.

Additional details for the completed and ongoing studies are summarized in Table 34 and Table 35 of Appendix 7.

Table 11: Overview of Clinical Study Vaccines, Populations and Status as of the PBRER No.06 DLP (19-Dec-2024)

Study ID **Study Location**	**Study Vaccine(s) / 2-Dose Primary Series, Booster or Single Dose**	**Study Population**	**Status**
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 (2 parts were completed of the original 4 Parts)			
2019nCoV-301 Adolescent Main US	Prototype (NVX-CoV2373) / Primary series	Adolescents 12 years to < 18 years	Completed
2019nCoV-301 Adolescent Booster US	Prototype (NVX-CoV2373) / Homologous booster	Adolescents 12 years to < 18 years	Completed
2019nCoV-311 (1 part was completed of the original 2 parts)			
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	Completed

Table 11: Overview of Clinical Study Vaccines, Populations and Status as of the PBRER No.06 DLP (19-Dec-2024)

Study ID Study Location	Study Vaccine(s) / 2-Dose Primary Series, Booster or Single Dose	Study Population	Status
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.	Completed
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.	Completed
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	Completed
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.	Completed

Table 11: Overview of Clinical Study Vaccines, Populations and Status as of the PBRER No.06 DLP (19-Dec-2024)

Study ID Study Location	Study Vaccine(s) / 2-Dose Primary Series, Booster or Single Dose	Study Population	Status
2019nCoV-315 US	Monovalent: JN.1 variant (NVX-CoV2705)	Approximately 60 participants will receive a single dose of NVX-CoV2705 on Day 0 and remain on study until Day 28 for immunogenicity with safety data collection up to 180 days post-vaccination.	Ongoing
2019nCoV-415 US	2024-2025 NVX COVID-19 vaccine (NVX-CoV2705) or 2024-2025 Pfizer-BioNTech mRNA COVID-19 vaccine (Comirnaty)/Booster	Approximately 660 health care workers and first responders who intend to get an updated 2024-2025 COVID-19 vaccine during Fall/Winter 2024-2025	Ongoing
2019nCoV-503 Dominican Republic, Guatemala, Honduras, Mexico, Philippines, US	Prototype (NVX-CoV2373) / Primary series Prototype (NVX-CoV2373), NVX-CoV2601 or NVX-CoV2705) / Booster	Children 6 years to < 12 years, 2 years to < 6 years, and 6 months to < 24 months	Ongoing

7.1 Completed Clinical Trials

As of the DLP for this PBRER (19-Dec-2024), the following clinical trials were completed (i.e., a final CSR was prepared): Study 2019nCoV-301 Adolescent Main and Adolescent Booster (two parts of the 4-part clinical trial); Study 2019nCoV-311 Part 2 (the second part of a 2-part clinical trial); Study 2019nCoV-312; Study 2019nCoV-313 Part 1; Study 2019nCoV-313 Part 2 (both parts of a 2-part clinical trial); and Study 2019nCoV-314.

Summaries of clinically important immunogenicity and safety results obtained from final CSRs are presented below. No new clinically important safety information emerged from these trials during the reporting interval.

7.1.1 Study 2019nCoV-301 Adolescent Primary Series (Main) and Adolescent Booster

The following information was obtained from the final CSR for the Adolescent Primary Series (Main) and Adolescent Booster of Study 2019nCoV-301 (dated 24-Sep-2024), which presents the final (24-month) analysis of efficacy, immunogenicity and safety data as of the last patient visit on 31-Aug-2023, with database lock on 27-Dec-2023.

Study 2019nCoV-301 was a Phase 3, multinational, multicentre, randomized, observer-blinded, placebo-controlled study evaluating the efficacy, effectiveness, safety, and immunogenicity of 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 in the US. This study also included a Booster Amendment and Second Booster Vaccination Sub-study, which allowed for the evaluation of first and second booster doses of NVX-CoV2373, respectively.

In the Paediatric Expansion, adolescent participants 12 to < 18 years of age were enrolled without further stratification, although the sites were instructed to recruit a similar number of participants in the 12 to < 15 years and 15 to < 18 years subgroups. Approximately 3,000 adolescent participants were randomized in a 2:1 ratio via block randomization to receive 2 intramuscular (IM) injections of NVX-CoV2373 or placebo (normal saline). Enrolment of the full cohort of adolescent participants was contingent upon the review of early safety data (i.e., 7 days of reactogenicity and overall safety post-Dose 1) from the first ~60 enrolled participants (randomized in a 2:1 ratio to receive NVX-CoV2373 or placebo, equally distributed between the age subgroups: 12 to < 15 years of age and 15 to < 18 years of age) before enrolment of the remainder of the adolescent participants (N = ~2,940). Likewise, administration of the second vaccine dose to the full participant population was contingent upon the review of early safety data (i.e., 7 days of reactogenicity and overall safety post-Dose 2) from the first ~60 enrolled participants before dosing the remainder of the participants. Safety data were provided to and reviewed by the Data and Safety Monitoring Board (DSMB) after each early safety data review period (i.e., 7 days after each vaccination in the sentinel group). Simultaneously, safety data were reviewed internally by the Sponsor.

Adolescent participants were enrolled at selected sites in the US, with an effort to recruit from a diverse population including underserved minorities.

The results of the Adult Main Study were presented in a separate CSR that was summarized in PBRER Number 05 (20-Dec-2023 to 19-Jun-2024).

The Paediatric Expansion of Study 2019nCoV-301 was initiated on 26-Apr-2021 (first participant screened) and completed enrolment into the initial vaccination period on 05-Jun-2021. The blinded crossover vaccination period was initiated on 06-Aug-2021 and the first and second booster vaccination periods were initiated on 04-Apr-2022 and 06-Feb-2023, respectively. The date of the last participant, last visit (LPLV) for the final (24-month)

analysis for the Paediatric Expansion of Study 2019nCoV-301 was 31-Aug-2023, with database lock on 27-Dec-2023.

The calendar period during which these data were collected represented a challenging backdrop for the conduct of a randomized clinical trial. Enrolment and dosing commenced on 26-Apr-2021. On 11-Dec-2020, EUA COVID-19 vaccinations had become available for adolescents who were 16 years of age and older. Over the subsequent months, EUA vaccines became available for larger groups of the public until 10-May-2021, when EUA vaccines were available for individuals 12 through 15 years of age and in the following year booster doses were recommended for adolescents in a fashion similar to those recommendations for adults.

The data presented in this final report represent the clinical data from the Paediatric Expansion of Study 2019nCoV-301. This report included all efficacy, effectiveness, immunogenicity, and safety data accumulated from the initiation to completion of the study, including 2 years of safety follow-up after the initial vaccination period. Additionally, the final data from the first and second booster vaccination periods, including solicited AEs in the 7 days after the booster doses, unsolicited AEs up to 28 days after booster vaccination and immunogenicity at 28 days after booster vaccination. Safety data including 6 months follow-up after booster vaccination are also provided. Because of the availability of EUA vaccination for all adolescents in the US, a blinded crossover was implemented as had been introduced in the Adult Main Study of Study 2019nCoV-301 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. This strategy proved successful in that 82.5% of the enrolled adolescent participants were retained in follow-up at 12 months after the primary vaccination series.

7.1.1.1 Efficacy and Effectiveness Conclusions

This data presented in the final report presents the full efficacy dataset of all participants with protocol-defined primary endpoint cases of polymerase chain reaction (PCR)-confirmed mild, moderate, or severe COVID-19 occurring at least 7 days after the completion of the primary vaccination series (denoted as the initial vaccination period). This period of case accrual coincided with the summer of 2021, during which the Delta variant was the predominant circulating strain. Thus, the demonstration of 79.54% protective efficacy (95% confidence interval (CI): 46.83, 92.13) was a clinically meaningful degree of efficacy.

The efficacy demonstrated across most demographic subsets of the efficacy population was similar to the overall Per Protocol Efficacy (PP-EFF) population. Similarly, the primary effectiveness analysis that evaluated the neutralizing antibody responses to the primary vaccination series in adolescents compared with that in young adults 18 to < 26 years from the Adult Main Study, in whom clinical efficacy had been demonstrated earlier, met the criteria for non-inferiority; thus, protective efficacy can also be inferred from the bridging of immune

responses. Again, the immune responses across most demographic subsets were also comparable to those in the overall Per Protocol Immunogenicity (PP-IMM) population.

At the time of first booster vaccination, the overall antibody levels (by neutralizing antibody assay or others) had declined by approximately 95% from the peak 14 days after the completion of the primary series (similar to the finding in adults). Administration of a single booster injection at the same dose used for the primary series resulted in neutralizing antibody levels 28 days later that were markedly higher than those observed after the primary series: Geometric Mean Titer (GMT) of 11824.4 (95% CI: 8993.1, 15546.9) versus GMT of 4434 (95% CI: 3658.0, 537.5) with an increase after the booster of 2.7 over the peak post-primary series level. This level of neutralizing antibody titers can be inferred to provide a high level of protective efficacy, both on the basis of observed efficacy results from this study and on the correlates of protection against both the ancestral (Wuhan) strain and the Delta variant defined from the adult portion of the study [Fong 2023].

7.1.1.2 Safety conclusions

The safety of both the primary vaccination series and the booster injections, in terms of solicited as well as unsolicited treatment emergent adverse events (TEAEs) was similar to that described in adults in this and other clinical trials. Local injection site pain and tenderness, usually mild to moderate in intensity, in the 1 to 2 days following injection was common (generally reported by > 50% of participants). These signs/symptoms were reported with increasing frequency, but not different intensity or duration, after second and third doses, but did not increase further following the subsequent fourth dose.

Solicited systemic reactions of headache, fatigue, malaise, and myalgia were reported by ~30% of participants after the first dose, with slightly increasing frequencies after the second and third doses. These reported events were also generally of mild-to-moderate intensity and of 1 to 2 days duration after any of the 3 doses. Notably, fever was infrequent and of short duration after any dose in both the older (15 to < 18 years) and younger (12 to < 15 years) adolescent age groups.

Unsolicited TEAEs were reported from in approximately 16% of participants and were evenly distributed across the treatment groups during the initial vaccination period. Fewer than 3% of AEs were considered by investigators as related to trial vaccine, and there were no deaths. One serious unexpected suspected adverse reaction (SUSAR) was reported, an event of myocarditis during the blinded crossover vaccination period. There were very few medically attended adverse events (MAAEs) attributed to trial vaccine, and only 1 event of headache considered to be a treatment-related event that led to withdrawal from the study. There was 1 case of myocarditis reported during the post-crossover vaccination period and none reported during the initial and booster vaccination periods. The case was of short duration and self-limited, resolving without sequelae. No cases of anaphylaxis were reported.

7.1.1.3 Overall conclusions of Study 2019nCoV-301 Adolescent Primary Series (Main) and Adolescent Booster

In conclusion, the results of the primary vaccination series with NVC-CoV2373 in adolescents 12 to < 18 years of age demonstrated a high degree of protective efficacy, even though the predominant circulating strain of SARS-CoV-2 was the Delta variant. A robust immune response, in terms of neutralizing antibody titers as well as anti-S IgG levels and human angiotensin converting enzyme 2 (hACE2) receptor inhibiting antibody levels, was demonstrated following the primary series.

While all antibody titers declined significantly in the 6 to 12 months following the primary series, a single booster dose of the same dose level and volume based on the ancestral (Wuhan) strain of SARS-CoV-2 induced a very robust response against the Wuhan strain and cross-reacting antibodies against subsequent variants, including Omicron BA.1 and BA.5 subvariants. These responses raised the antibody levels to well in excess of those levels associated with protective efficacy. At the same time, the vaccine was safe and well tolerated in terms of both solicited and unsolicited TEAEs, which were not notably different after multiple doses of vaccine.

It is concluded that this study supports the efficacy and safety NVX-CoV2373 as a primary vaccination series and subsequent periodic single doses in adolescents 12 to < 18 years of age. The immunogenicity and safety after the booster doses support of the use of the vaccine as a single injection in adolescents consistent with evolving public health recommendations for periodic updated vaccinations.

7.1.2 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

The following information was obtained from the final CSR for Part 2 of Study 2019nCoV-311 which presents immunogenicity and safety data from the first dose of study vaccine through Day 270 with a data extraction date of 05-Apr-2024 and Last Patient Last Visit on 11-Feb-2024.

Study 2019nCoV-311 was a 2-Part, Phase 3, randomized, observer-blinded study evaluating the safety and immunogenicity of Omicron subvariant vaccines in previously vaccinated adults conducted in Australia. Part 1 is complete and evaluated the immunogenicity and safety of a single booster dose of NVX-CoV2515 and NVX-CoV2373 (prototype) alone and bivalent prototype and Omicron BA.1 subvariant vaccine in previously vaccinated (i.e., 2 or 3 doses of the Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines) adults 18 to 64 years of age (inclusive). Part 2 is complete and evaluated the immunogenicity and safety of 2 booster doses of NVX-CoV2540 and NVX-CoV2373 alone and bivalent prototype and Omicron

BA.5 subvariant vaccine in previously vaccinated (i.e., ≥ 3 doses of the Moderna and/or Pfizer-BioNTech prototype COVID-19 vaccines) in adults ≥ 18 years of age.

Part 2 of Study 2019nCoV-311 was initiated on 22-Mar-2023 (first participant screened) and completed enrolment on 02-May-2023. A planned 28-day interim analysis was performed with a data cutoff date of 31-May-2023. Briefly, each of the 3 co-primary endpoints was achieved, demonstrating that the bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induced superior neutralising antibody (NAb) responses compared to the prototype Novavax NVX-CoV2373 vaccine in participants previously vaccinated with ≥ 3 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent mRNA COVID-19 vaccines. The bivalent vaccine induced superior NAb responses compared to NVX-CoV2373 against the Omicron BA.5 subvariant as measured by between-group geometric mean titer ratio (GMTR) of inhibitory dilution at a concentration of 50% (ID50) GMTs (adjusted) and non-inferior seroresponse rate at Day 28. The NVX-CoV2540 vaccine alone and as a bivalent formulation with NVX-CoV2373 induced a broad range of neutralizing and anti-S immunoglobulin G (IgG) antibodies, generating the highest antibody levels against the Omicron BA.5 subvariant versus that seen 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 monovalent and/or bivalent mRNA COVID-19 vaccines.

7.1.2.1 Immunogenicity Conclusions

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, Day 104, and Day 118 using a validated pseudovirus neutralization assay (Novavax Clinical Immunology).

All 3 co-primary endpoints were achieved in Part 2 of the study. 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 versus 515.1, respectively) at Day 28, with a GMTR of 2.0 (95% CI: 1.69, 2.33) and a lower bound 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 seroresponse rate against the Omicron BA.5 subvariant pseudovirus versus NVX-CoV2373 (39.8% vs 12.3%, respectively) at Day 28, with a difference in seroresponse rates of 27.5% (95% CI: 19.8, 35.0) and a lower bound 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 bound 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.

Overall, NAb responses increased initially from baseline to peak response after initial booster vaccination, declined sharply thereafter through Day 90 and, after a second booster vaccination at Day 90, further increased substantially, exceeding the initial peak response, and then declined through Day 270.

Age-related patterns of pseudovirus neutralization for NVX-CoV2540 , NVX-CoV2373, and bivalent vaccine against the Omicron BA.5 subvariant pseudovirus, the Omicron XBB.1.5 subvariant pseudovirus, and the ancestral (Wuhan) pseudovirus were similar for all participants regardless of age; NAb levels were generally higher for younger (18 to 54 years) versus older (≥ 55 years) participants but this could be attributed to higher neutralization responses at baseline for the younger participants since no overall difference in geometric mean fold rise (GMFR) between younger and older participants was apparent.

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.

It should be noted that NAb results for the subset of participants tested with the Monogram Biosciences assay as an exploratory endpoint as well as for the microneutralization assay of the dilution to achieve 50% neutralization (MN_{50}) NAb assay were consistent with those obtained with the Novavax Clinical Immunology pseudovirus neutralization assay.

The anti-S IgG and hACE2 receptor binding inhibition responses overall after vaccination with bivalent vaccine, NVX-CoV2373, and NVX-CoV2540 generally followed the same trend as that seen for NAb responses with these vaccines.

Compared to the prototype vaccine, the updated Omicron subvariant vaccines (either as monovalent or bivalent vaccinations combined with the prototype [Wuhan] vaccine) elicited higher pseudovirus NAbs to the more contemporaneous variants of concern. This effect also noted in the IgG and hACE2 receptor binding inhibition would suggest that the updated vaccines are more effective in providing protection to matched strains than the prototype (Wuhan) vaccine.

As expected, the antibody titers were higher in younger populations and in those who had laboratory evidence of prior infection as noted by anti-N positivity at baseline. Interesting to note, the immune response in participants with 3 prior vaccinations was higher than that in participants with ≥ 4 prior vaccinations. This might be explained that by having 3 shots, and a considerably longer time since their last dose before study vaccine, participants with 3 shots

had better maturity of their immune system and therefore could mount higher titers of NAbs (Gilboa 2022).

Although participants had previously received ≥ 3 doses of mRNA COVID-19 vaccines the immune responses at 3 months (Day 90) after the initial vaccination in this study remained well above baseline (Day 0) for NVX-CoV2540 and the bivalent vaccine indicating a good level of persistence of the response. A similar pattern of persistence was seen at 6 months (Day 270) after the second vaccination, with NAb levels often remaining above baseline at that time point.

Antigen-specific Cluster of Differentiation 4+ (CD4+) cell (effector memory) levels after stimulation with different protein antigens were evaluated in a separate exploratory analysis. Geometric mean cell counts were higher after vaccination with NVX-CoV2540 versus that with NVX-CoV2373. Stimulation with BV2601-XBB.1.5 protein yielded a higher GM cell count of Type 1 helper (Th1) cytokines interferon gamma+ (IFNγ+)) tumour necrosis factor alpha+ (TNFα+), and interleukin 2+ (IL-2)+ CD4+ T cells versus stimulation with other protein antigens (eg, SARS-CoV-2 rS Vaccine BV2373-Wuhan, BV2540-BA.5). In general, Th1 responses were stronger than those for Type 2 helper (Th2) cytokines.

7.1.2.2 Safety Conclusions

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

Safety objectives included an assessment of overall safety after initial and second vaccinations for all unsolicited AEs, MAAEs, related MAAEs (ie, 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%). In a sub-analysis stratified by age, the frequency of participants 18 to 54 years of age with any solicited AE after initial booster vaccination, was higher (range of 78.0 to 81.1% between study vaccine groups) than that seen for participants ≥ 55 years of age (range of 55.8 to 68.1% between study vaccine groups) and higher for younger participants after second booster vaccination, (range of range of 73.1 to 74.8% between study vaccine groups) versus that seen for older participants (range of 60.0 to 65.1% between study vaccine groups).

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) in the bivalent vaccine group.

Unsolicited AEs after initial and second booster vaccination were similar overall between the 3 study vaccine groups (overall range between 19.7 to 26.7%). In a sub-analysis stratified by age, frequencies of unsolicited AEs through 28 days after initial booster vaccination were similar for participants 18 to 54 years of age and ≥ 55 years of age but higher for younger versus older participants after second booster vaccination. The frequency of participants with unsolicited AEs through 28 days after initial booster vaccination among White participants (range 22.8 to 26.3%) was similar to that seen for the overall population. However, Asian participants reported a relatively high frequency of unsolicited AEs after initial booster vaccination with NVX-CoV2373 (31.3%) versus that after initial booster vaccination with NVX-CoV2540 (2.8%) or the bivalent vaccine (11.5%).

Most unsolicited AEs were mild or moderate in severity and not related to study vaccine. Few participants had SAEs (overall range between 0.4 to 2.0%) between study vaccine groups; 1 (0.4%) participant had a related SAE of IVth nerve paralysis that occurred from initial vaccination to second vaccination in the NVX-CoV2540 group. No participant had an SAE with an outcome of death in this study. Adverse event of special interest (AESI): Potential immune mediated medical conditions (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.

7.1.2.3 Overall Conclusions for Completed Study 2019nCoV-311 Part 2

The overall conclusions of the final immunogenicity and safety analyses through Day 270 are:

- The bivalent vaccine (NVX-CoV2373 + NVX-CoV2540) induced superior antibody responses following first booster vaccination compared to the antibody responses induced by NVX-CoV2373.
- NVX-CoV2540 induced statistically significant 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.

7.1.3 Study 2019nCoV-312

A Phase 3 Study to Evaluate the Immunogenicity and Safety of Novavax COVID-19 Vaccine(s) as Second or Subsequent Boosters After mRNA Vaccines in Individuals 18 to 49 Years of Age

The following information was obtained from the final CSR for Study 2019nCoV-312 which presents immunogenicity and safety data of ancestral strain NVX-CoV2373 and an updated Novavax vaccine based on recent variant(s) when used as a second booster dose in individuals who have previously received two or three doses of licensed mRNA vaccines followed by one booster with ancestral strain NVX-CoV2373 vaccine.

Study 2019nCoV-312 was an open-label Phase 3 study evaluating the immunogenicity and safety of Novavax vaccine(s) with Matrix-M™ adjuvant (ancestral strain NVX-CoV2373 and an alternative strain and/or multivalent Novavax vaccine) as booster doses following a series of primary and/or booster doses of authorized/approved messenger ribonucleic acid (mRNA) vaccines followed by a single booster dose of NVX-CoV2373 in the Novavax 2019nCoV-307 study (Study 307). This study enrolled up to 150 adult participants 18 to 49 years of age who previously participated in Study 307. Approximately 100 participants received 1 dose of ancestral strain NVX-CoV2373 vaccine, given on Day 1, at a dose level of 5 µg of ancestral strain antigen with 50 µg of Matrix-M adjuvant. Subsequently, approximately 50 additional participants were enrolled to receive 1 dose of an updated Novavax vaccine based on recent variant (BA.5) at a dose level of 5 µg total antigen with 50 µg of Matrix-M adjuvant, that is, NVX-CoV2540.

All participants remained on study for assessment of immunogenicity at Day 29 and safety data collection through 6 months (Day 181) following the vaccination.

7.1.3.1 Immunogenicity Conclusions

This open label Phase 3 study evaluated the immunogenicity of booster doses of NVX-CoV2373 and NVX-CoV2540 after primary and booster doses of authorized/approved mRNA vaccines followed by a single booster dose of NVX-CoV2373 in Novavax 2019nCoV-307 study (Study 307). The study met the primary endpoints; when Day 29 immunogenicity results for participants who received a booster dose of NVX-CoV2373 in Study 312 compared to results in Study 307, the primary endpoints of non-inferiority and superiority were met. For the participants who received the updated NVX vaccine (NVX-CoV2540, Omicron BA.5), non-inferiority and superiority between booster doses at Day 29 from Study 312 and Study 307 were demonstrated as a descriptive endpoint.

Secondary immunogenicity descriptive endpoints of non-inferiority were achieved based on seroconversion rate as well as IgG ELISA unit concentrations (GMEU/mL) and hACE2 antibodies to the SARS CoV-2 spike protein (Wuhan) after a booster dose of the updated NVX vaccine following mRNA vaccines.

As an exploratory endpoint, an analysis of immunogenicity was also conducted based on COVID vaccine history. Several recent studies have indicated that heterologous dosing for COVID-19 may induce comparable or higher antibody titers and a similar reactogenicity profile to homologous regimens [Garg 2022]. For this reason, the Center for Disease Control and Prevention has issued guidance supporting a heterologous boosting COVID-19 vaccine strategy. For the most part, NVX-CoV2373 and NVX-CoV2540 increased nAb titers regardless of the vaccine history in this study; however, no direct comparisons were made.

7.1.3.2 Safety Conclusions

Both NVX-CoV2373 and NVX-CoV2540 were found to have an acceptable safety profile in this study. The incidence of solicited reactions was similar between the NVX-CoV2373 group (77.9%) compared with the NVX-CoV2540 group (74.4%). No participants receiving NVX-CoV2373 and 1 (2.3%) participant in the updated NVX vaccine group experienced a serious TEAE through the study. There was one reported MAAE (medically attended adverse event) (postprocedural hematoma), no AESIs (PIMMCs), no AESIs related to COVID-19, no cases of myocarditis/pericarditis, and no TEAEs related to study discontinuation.

Based on the results of this study, we conclude that booster doses of NVX-CoV2373 and NVX-CoV2540 provide immunogenicity against both the Wuhan and Omicron BA.5 strains of COVID-19. Although further studies are needed, this study also indicated that immunogenetic responses are not negatively affected by heterologous dosing with NVX-CoV2373 and NVX-CoV2540 after primary mRNA doses.

7.1.4 Study 2019nCoV-313 Part 1

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, Phase 2/3 Study of Safety and Immunogenicity of an Omicron XBB.1.5 Subvariant Vaccine

The following information was obtained from the final CSR for Part 1 of Study 2019nCoV-313 which presents the final analysis of Part 1 of Study 2019nCoV-313 as of the last participant, last visit date of 01-Apr-2024 and data extraction date of 10-May-2024. This report also summarizes the immunogenicity results of the planned Day 28 interim analysis. Results of the final analysis of Part 2 of Study 2019nCoV-313 were presented in a separate CSR as summarized below in Section 7.1.5.

Study 2019nCoV-313 was a 2-part, Phase 2/3 open-label, single-arm study evaluating the safety and immunogenicity of a booster dose of NVX-CoV2601 in adult participants ≥ 18 years of age (Part 1) previously vaccinated with messenger ribonucleic acid (mRNA) COVID-19 vaccine and in baseline SARS-CoV-2 seropositive COVID-19 vaccine naïve participants ≥ 18 years of age (Part 2) in the US and its territories. In Part 1 and Part 2 of the study, participants received booster vaccination on Day 0 and were followed for immunogenicity and safety data collection through Day 180 with interim analyses planned at Day 28.

Part 1 of Study 2019nCoV-313 was initiated on 07-Sep-2023 (first participant screened) and completed enrolment on 08-Sep-2023. A planned Day 28 interim analysis of all primary and secondary immunogenicity endpoints and safety analysis through the data cutoff date was performed with a data cutoff date of 16-Oct-2023 and a data extraction date of 17-Jan-2024;

results of the planned Day 28 interim analysis were presented in the 2019nCoV-313 Part 1 Interim Analysis (Version 1.0, dated 29-Mar-2024). Briefly, the results of the planned Day 28 interim analysis showed that both co-primary endpoints were achieved in Part 1 of Study 2019nCoV-313 and a booster dose of NVX-CoV2601 was well tolerated with an acceptable safety profile.

7.1.4.1 Immunogenicity Conclusions

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 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 NVX-CoV2373 (data derived from Group G of Part 2 of Study 2019nCoV-311 conducted in Australia approximately 6 months prior to the start of Study 2019nCoV-313) and (2) to determine if NVX-CoV2601 booster induced noninferior seroresponse rates compared to seroresponse rates of a historical control of NVX-CoV2373 in participants who previously received ≥ 3 mRNA COVID-19 vaccinations.

A total of 332 participants were enrolled in the study at 30 sites in the US and its territories. Data from 1 site (Site US263) was not used in any of the analyses due to data compliance issues.

Both co-primary endpoints were achieved in Part 1 of Study 2019nCoV-313, with the first co-primary endpoint demonstrating superiority of the NVX-CoV2601 booster compared to the historical control NVX-CoV2373 booster against the Omicron XBB.1.5 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 noninferiority of the NVX-CoV2601 booster compared to the historical control NVX-CoV2373 booster for the difference in seroresponse rates at Day 28 when the lower limit of the 95% CI for the difference between the 2 booster vaccines exceeded -10% (50.5%). The seroresponse rates 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 seroresponse rates was 57.2% (95% CI: 50.5, 63.2).

The historical control group of NVX-CoV2373 booster used in Part 1 of this study was derived from Group G (N = 251 of treated participants) in Part 2 of Study 2019nCoV-311, a 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 nonpregnant 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.

Secondary immunogenicity endpoints evaluated immunogenicity data through Day 180. Pseudovirus neutralization (ID50) GMTs at baseline, Day 28, and Day 180 were 120.7, 955.5, and 454.8, respectively. Based on ID50 GMTs, percent change from baseline to Day 28 was 691.5%, and percent change from baseline to Day 180 was 276.8%. The percent change from Day 28 to Day 180 was -52.4%. The GMFR between baseline and Day 180 was 3.8. The approximately 50% immune response reduction observed 6 months post-vaccine administration is consistent with expectations, as similar trends have been previously reported for this vaccine and by mRNA vaccines. The gradual decline in immune response over time is a well-documented characteristic of vaccine-induced immunity.

When subgroup analyses were performed, serum NAbs (ID50) against the Omicron XBB.1.5 pseudovirus, NVX-CoV2601 induced similar responses in participants 18 to 54 years of age and participants ≥ 55 years of age, in participants receiving prior doses of Pfizer-BioNTech, Moderna, and Moderna + Pfizer-BioNTech, regardless of the variant of the prior vaccine and regardless of baseline anti-N status.

Anti-rS IgG antibody response was evaluated against the Omicron XBB.1.5 rS protein. From Day 0 (baseline) to Day 28, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased from 23771.4 to 83205.7 EU/mL (ELISA Units per mL). From Day 0 (baseline) to Day 180, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased to 45388.2 EU/mL. The GMFR between baseline and Day 28 was 3.5. The GMFR between Day 0 (baseline) and Day 180 was 1.9. As expected, seroresponse rates were also higher from Day 0 (baseline) to Day 28 (39.7%) and from Day 0 (baseline) to Day 180 (17.5%). These results were also consistent across subgroups.

As an exploratory endpoint, serum NAb titers against the ancestral Wuhan pseudovirus and anti-S IgG antibody responses against the ancestral Wuhan S protein were evaluated. For serum NAb titers, GMTs (ID50) were 1294.6 at Day 0 (baseline), 2272.4 at Day 28, and 1374.0 at Day 180. Seroresponse rates from Day 0 (baseline) to Day 180 was 10.3%. GMTs (ID50) and seroresponse rates were similar between age groups.

7.1.4.2 Safety Conclusions

NVX-CoV2601 was well tolerated with an acceptable safety profile following booster vaccination in adult participants ≥ 18 years of age who had previously received ≥ 3 mRNA prototype COVID-19 mRNA vaccines.

Solicited local injection site TEAEs were reported in 189 (56.9%) participants within 7 days following booster vaccination, with higher, with higher frequencies in participants 18 to 54 years of age (64.2%) than in participants ≥ 55 years of age (48.7%). Most solicited local injection site TEAEs were grade 1 in severity, with 1 (0.3%) participant reporting a grade 3 event and no participant reporting a grade 4 event. Pain/tenderness were the most frequent solicited local injection site TEAEs.

Solicited systemic TEAEs were reported in 158 (47.6) participants within 7 days following booster vaccination, with higher frequencies in participants 18 to 54 years of age (51.7%) than in participants ≥ 55 years of age (42.9%). Most solicited systemic TEAEs were grade 1 or grade 2 in severity, with 4 (1.2%) participants reporting grade 3 events and no participant reporting a grade 4 event. Fatigue/malaise, muscle pain, and headache were the most frequent solicited systemic TEAEs.

Unsolicited TEAEs through 28 days after booster vaccination were reported in < 10% of participants, with most unsolicited TEAEs being mild or moderate in severity and not related to study vaccine. SAEs were reported in < 2% of participants, none of which were related to study vaccine. There were no deaths, AESIs (PIMMC or COVID-19 related), TEAEs of myocarditis/ pericarditis, or TEAEs leading to study discontinuation.

7.1.4.3 Overall Conclusions for Completed Study 2019nCoV-313 Part 1

The overall conclusions of this analysis are:

- The co-primary endpoints of the study were achieved, as the Omicron XBB.1.5 subvariant vaccine NVX-CoV2601 induced a superior nNb response in adjusted GMT (ID50) against the Omicron XBB.1.5 subvariant virus along with a noninferior seroresponse rate 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.
- NAb responses (ID50) and anti-rS IgG antibody responses against the Omicron XBB.1.5 subvariant virus remained evident through Day 180 of this study.
- 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.

7.1.5 Study 2019nCoV-313 Part 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, Phase 2/3 Study of Safety and Immunogenicity of an Omicron XBB.1.5 Subvariant Vaccine

The following information was obtained from the final CSR for Part 2 of Study 2019nCoV-313 which presents the final analysis of Part 2 of Study 2019nCoV-313 as of the last participant, last visit (LPLV) date of 20-May-2024 and data extraction date of 09-Jul-2024. This report also summarizes the immunogenicity results of the planned Day 28 interim analysis and summarizes changes in safety data between the planned interim and final analysis.

Part 2 of Study 2019nCoV-313 was initiated on 18-Sep-2023 (first participant screened) and completed enrollment on 15-Nov-2023. The co-primary objectives in Part 2 were 1) to determine if a single dose of NVX-CoV2601 in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induced noninferior seroresponse rates to the Omicron XBB.1.5 subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants (Part 1 of Study 2019nCoV-313) and 2) to determine if a single dose of NVX-CoV2601 in SARS-CoV-2 seropositive COVID-19 vaccine naïve participants induced noninferior antibody responses to the Omicron XBB.1.5 subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVD-19 mRNA vaccinated participants (Part 1 of Study 2019nCoV-313). A planned Day 28 interim analysis of all primary and secondary immunogenicity endpoints and safety analysis through the data cutoff date was performed with a data cutoff date of 19 December 2023 and a data extraction date of 21-Feb-2024. Briefly, the results of the planned Day 28 interim analysis showed that both co-primary endpoints were achieved in Part 2 of Study 2019nCoV-313 and single-dose administration of NVX-CoV2601 was well tolerated with an acceptable safety profile.

Results of the final analysis of Part 1 of Study 2019nCoV-313 were presented in a separate CSR as described above in Section 7.1.4.

7.1.5.1 Immunogenicity Conclusions

Both co-primary endpoints were achieved in Part 2 of Study 2019nCoV-313, with the first co-primary endpoint demonstrating noninferior seroresponse rates to the XBB.1.5 Omicron subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants. Additionally, as assessed by the ratio of their NAb GMTs (ID50), a single dose of NVX-CoV2601 vaccine on SARS-CoV-2 seropositive COVID-19 vaccine-naïve participants induced noninferior antibody responses to the XBB.1.5 Omicron subvariant compared to those of a booster dose of NVX-CoV2601 in previously COVID-19 mRNA vaccinated participants.

Study participants provided an additional blood sample at Day 180 to assess the post-immunization antibody kinetics overtime. Although the antibody titers decreased over the period of 6 months, those titers were still substantially higher than baseline. Seroresponse rates from baseline to Day 28 were 74.3% (95% CI: 68.9%, 79.3%) and from baseline to Day 180 were 45.0% (95% CI: 38.8%, 51.4%). Based on ID50 GMTs, percent change from baseline to Day 28 was 1835.2% and percent change from baseline to Day 180 was 353.0%.

When subgroup analyses were performed, serum neutralizing antibodies against the Omicron XBB.1.5 subvariant pseudovirus, NVX-CoV2601 induced similar responses in participants 18 to 54 years of age and participants ≥ 55 years of age.

Anti-rS IgG antibody response was evaluated against the Omicron XBB.1.5 rS protein. From baseline (Day 0) to Day 28, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased from 5188.1 (95% CI: 4342.1, 6198.9) to 46961.6 (95% CI: 42046.8,

52450.9). From baseline to Day 180, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased to 14606.7 (95% CI: 12772.3, 16704.6). The GMFR between baseline and Day 28 was 9.0 (95% CI: 7.6, 10.7). The GMFR between baseline and Day 180 was 2.8 (95% CI: 2.4, 3.4). As expected, seroresponse rates were also higher from baseline to Day 28 (68.4% [95% CI: 62.7%, 73.7%]) vs baseline to Day 180 (38.2% [95% CI: 32.2, 44.6%]). From baseline (Day 0) to Day 28, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased from 23771.4 (95% CI: 21110.0, 26768.4) to 83205.7 (95% CI: 74747.0, 92621.6). From baseline to Day 180, anti-rS IgG antibody GMEUs against the Omicron XBB.1.5 rS protein increased to 45388.2 (95% CI: 40799.3, 50493.2).

7.1.5.2 Safety Conclusions

Regarding safety, 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 TEAEs were reported in 140 (41.4%) participants within 7 days following single dose vaccination with NVX-CoV2601 in COVID-19 vaccine naïve participants, with higher frequencies in participants 18 to 54 years of age (43.3%) than in participants ≥ 55 years of age (31.5%). Most solicited local injection site TEAEs were grade 1 or grade 2 in severity, with 3 (0.9%) participants reporting a grade 3 event (tenderness) and no participant reporting a grade 4 event. Pain/tenderness were the most frequent (incidence > 20%) solicited local injection site TEAEs.

Solicited systemic TEAEs were reported in 164 (48.5%) participants within 7 days following single dose vaccination with NVX-CoV2601 in COVID-19 vaccine naïve participants, with higher frequencies in participants 18 to 54 years of age (49.3%) than in participants ≥ 55 years of age (44.4%). Most solicited systemic TEAEs were grade 1 or grade 2 in severity, with 7 (2.1%) participants reporting grade 3 events (fatigue, malaise, muscle pain, joint pain, nausea/vomiting and headache) and no participant reporting a grade 4 event; of note, the frequency of participants with grade 3 events was numerically higher in the older age group than in the younger age group (3.7% vs 1.8%, respectively). Fatigue/malaise, muscle pain, and headache were the most frequent (incidence > 20%) solicited systemic TEAEs. 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.

Eight (2.4%) participants reported at least 1 MAAE through 28 days after single dose vaccination with NVX-CoV2601 in COVID-19 vaccine naïve participants (Table 25). MAAEs of the SOC Infections and Infestations were the most frequent (incidence > 1%). No individual MAAE occurred in > 1 participant. No participant reported an AESI of PIMMC, an AESI relevant to COVID-19, or a TEAE of myocarditis/pericarditis after a single dose vaccination with NVX-CoV2601 in COVID-19 vaccine naïve participants (Part 2) through Day 180. SAEs were reported in <2% of participants, none of which were related to study vaccine.

7.1.5.3 Overall Conclusions for Completed Study 2019nCoV-313 Part 2

The overall conclusions of this analysis are:

- This study supports the indication of a single dose of a Novavax vaccine on the vaccine-naïve population. This study demonstrated that single dose of Novavax vaccine NVX-CoV2601 (recommended at the time of this study) was at least as immunogenic in the vaccine-naive population as the vaccine administered to a previously immunized [multiple times (≥ 3 doses)] population. NAb responses and anti-rS IgG antibody responses against the Omicron XBB.1.5 subvariant virus remained evident at Day 180 of this study, suggestive of the durability of the immune response generated by a single dose of the Omicron XBB.1.5 subvariant vaccine.
- NVX-CoV2601 was well tolerated, with an acceptable safety profile when used as a single dose vaccination in COVID-19 vaccine naïve participants through Day 180.

7.1.6 Study 2019nCoV-314

A Phase 3, Randomized, Double-Blind 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

The following information was obtained from the final CSR for Study 2019nCoV-314 which presents immunogenicity and safety data for Study 2019nCoV-314 as of the last participant, last visit date of 01-Apr-2024 and data extraction date of 17-May-2024. Immunogenicity and safety data are described through Day 180 for all study participants.

Study 2019nCoV-314 was a Phase 3, randomized, double-blind study evaluating the safety and immunogenicity of a booster dose of the Omicron XBB.1.5 subvariant vaccine (NVX-CoV2601) and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) in adolescents who had received a regimen of ≥ 2 doses of the Moderna and/or Pfizer-BioNTech monovalent and/or bivalent COVID-19 vaccines ≥ 90 days previously.

7.1.6.1 Immunogenicity Conclusions

NAbs (ID50) against the Omicron XBB.1.5 subvariant pseudovirus and the ancestral (Wuhan) pseudovirus were assessed at Day 0 (baseline), Day 28, Day 90, and Day 180 using a validated pseudovirus neutralization assay (Novavax Clinical Immunology).

The primary immunogenicity objective was to describe the NAb response induced by NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) in regard to the induction of NAbs against the Omicron XBB.1.5 subvariant pseudovirus as measured by ID50 GMTs and the between-group GMTRs of ID50 GMTs (adjusted) at Day 28.

The bivalent vaccine (Group B) induced an inferior NAb response in ID50 adjusted GMT versus NVX-CoV2601 (Group A) in regard to the induction of NAbs against the Omicron

XBB.1.5 subvariant pseudovirus (1569.49 vs 2489.35, respectively) using a validated Novavax Clinical Immunology pseudovirus neutralization assay at Day 28, with a GMTR of 0.6 (95% CI: 0.50, 0.79).

The secondary immunogenicity analyses aim to show the relative immune responses of study vaccination with NVX-CoV-2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) and the persistence of immune response through 6 months after study vaccination at baseline (Day 0).

NAb responses after study vaccination with NVX-CoV-2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 subvariant pseudovirus were higher at all time points after study vaccination with NVX-CoV2601 (Group A) versus the bivalent vaccine (Group B). At Day 28, ID50 GMTs against the Omicron XBB.1.5 subvariant pseudovirus increased 12.2-fold from baseline (Day 0) for NVX-CoV601 (2533.08) and 8.4-fold for the bivalent vaccine (1544.61). A robust level of persistence of response was seen with increases of 8.6- and 6.2-fold from baseline, respectively, at Day 90 and responses remaining above baseline at Day 180 with GMFRs referencing Day 0 of 6.0 and 4.7, respectively.

Anti-S IgG antibody responses after study vaccination with NVX-CoV-2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) against the Omicron XBB.1.5 subvariant S protein were higher at all time points after study vaccination with NVX-CoV2601 (Group A) versus the bivalent vaccine (Group B). At Day 28, GMEUs against the Omicron XBB.1.5 subvariant pseudovirus increased 3.9-fold from baseline (Day 0) for NVX-CoV601 (150232.9 EU/mL) and 3.4-fold for the bivalent vaccine (113031.9 EU/mL). A good level of persistence of response was seen with increases of 2.8- and 2.6-fold from baseline, respectively, at Day 90 and responses remaining above baseline at Day 180 with GMFRs referencing Day 0 of 1.9 and 1.9, respectively.

In exploratory analyses, patterns of NAb responses and anti-S IgG responses after study vaccination with NVX-CoV2601 (Group A) and the bivalent vaccine (Group B) against the ancestral (Wuhan) pseudovirus were less robust than those seen against Omicron XBB.1.5 subvariant pseudovirus and exhibited a lower persistence of response.

The mucosal anti-S IgA antibody responses at Day 28 against the Omicron XBB.1.5 subvariant spike protein were minimal and similar for NVX-CoV2601 versus the bivalent vaccine (adjusted GMTs of 9.32 ng/mL versus 9.04 ng/mL, respectively) with a GMTR for the comparison between groups of 1.0 (95% CI: 0.81, 1.16). The mucosal anti-S IgA antibody between-group comparison for responses against the ancestral (Wuhan) spike protein for NVX-CoV2601 versus the bivalent vaccine was similar to that seen for responses against Omicron XBB.1.5 subvariant spike protein.

In post-hoc analyses the NAb response against the Omicron XBB.1.5 subvariant pseudovirus at Day 28 was higher for NVX-CoV2601 versus a cohort of adolescent participants from the

historical control (NVX-CoV2373 from the 301 PEDS study) (adjusted ID50 GMTs of 2004.32 versus 164.91, respectively) with a GMTR for the comparison between groups of 12.2 (95% CI: 8.50, 17.38) while the NAb response against the ancestral (Wuhan) pseudovirus at Day 28 was lower for NVX-CoV2601 versus a cohort of adolescent participants from the historical control (NVX-CoV2373 from the 301 PEDS study) (adjusted ID50 GMTs of 3000.29 vs 5368.24, respectively) with a GMTR for the comparison between groups of 0.6 (95% CI: 0.44, 0.71).

7.1.6.2 Safety Conclusions

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

NVX-CoV2601 and NVX-CoV2373 + NVX-CoV2601 were well tolerated with an acceptable safety profile after study vaccination in adolescent participants who had previously received ≥ 2 vaccinations of Moderna and/or Pfizer-BioNTech prototype COVID-19 mRNA vaccines.

The frequency of participants with solicited local injection site AEs of any grade was higher for those in Group A (71.6%) versus those in Group B (66.7%) with a relatively low frequency (≤ 1.0%) of grade 3 AEs. Pain/tenderness was the most frequently reported solicited local injection site AE (71.1% and 66.2% of participants for Group A and Group B, respectively).

The frequency of participants with solicited systemic AEs of any grade was somewhat higher for those in Group A (61.1%) versus those in Group B (57.1%) with a relatively low frequency (≤ 1.4%) of grade 3 AEs. Muscle pain was the most frequently reported solicited systemic AE (41.6% and 35.7% of participants for Group A and Group B, respectively).

Frequencies of participants with solicited local injection site or systemic AEs of any grade, local injection site or systemic grade 3 AEs, or local injection site or systemic grade 4 AEs were notably lower for participants in either Group A or Group B than for participants in the post-hoc historical control (NVX-CoV2373 from the 301 PEDS study) (Group C).

Subgroup analyses were performed for solicited local injection site and systemic AEs according to sex, race, ethnicity, and number of prior COVID-19 mRNA vaccinations. Differences in the frequencies of these AEs (ie, for Group A versus Group B) were noted between each of these demographic subgroups (eg, male participants reported higher frequencies of solicited local injection site or systemic AEs for Group A versus Group B whereas the frequencies of these AEs in these vaccine groups were similar for female participants). The significance of the differences seen in the frequencies of solicited AEs between vaccine Group A and Group B within each subgroup could not be ascertained due to the small sample size.

Unsolicited AEs through 28 days after study vaccination were similar between Group A and Group B (13.2% to 11.9%, respectively) and higher than that in the historical control (NVX-CoV2373 from the 301 PEDS study) (5.3%); this difference was mainly driven by AEs of upper respiratory infection reported in Group A and Group B. Most unsolicited AEs were mild or moderate in severity and not related to study vaccine. Few participants had SAEs (2.1% to 0.5%, respectively). No participants reported severe related TEAEs, related SAEs, AESIs: PIMMCs, AESIs relevant to COVID-19, AEs of myocarditis/pericarditis, or AEs leading to study discontinuation. No unsolicited SAEs resulting in death occurred in this study.

Subgroup analyses were performed for unsolicited AEs, severe unsolicited AEs, related unsolicited AEs, SAEs, MAAEs, severe MAAEs, related MAAEs, and severe related MAAEs according to sex, race, ethnicity, and number of prior COVID-19 mRNA vaccinations. Differences in the frequencies AEs for Group A versus Group B were noted between certain demographic subgroups (eg, male participants differed from female participants in the incidence reported for severe unsolicited AEs, SAEs, and MAAEs; Hispanic or Latino participants differed from Not Hispanic or Latino participants in the incidence reported for unsolicited AEs, severe unsolicited AEs, related unsolicited AEs, and SAEs; Black or African American differed from White participants in the incidence reported for related unsolicited AEs; participants who received 2 prior COVID-19 mRNA vaccinations differed from those who received ≥ 3 prior COVID-19 mRNA vaccinations in the incidence reported for severe unsolicited AEs and related unsolicited AEs). The significance of the differences seen in the frequencies unsolicited AEs between vaccine Group A and Group B within each subgroup could not be ascertained due to the small sample size.

7.1.6.3 Overall Conclusions for Completed Study 2019nCoV-314

The overall conclusions of the final immunogenicity and safety analyses through Day 180 are:

- The monovalent vaccine NVX-CoV2601 induced higher neutralizing antibody responses following study vaccination compared to the neutralizing antibody responses induced by the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601).
- Neutralizing antibody responses persisted through Day 90, remaining above baseline at Day 180 following vaccination with NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601).
- NVX-CoV2601 and the bivalent vaccine (NVX-CoV2373 + NVX-CoV2601) were well tolerated with an acceptable safety profile when used as a heterologous booster dose in adolescent participants who had previously received ≥ 2 doses of COVID-19 mRNA vaccines.

7.2 Ongoing Clinical Trials

As of the DLP for this PBRER (19-Dec-2024), the following clinical trials were ongoing (i.e., final CSRs were not prepared): Study 2019nCoV-205; Study 2019nCoV-315; Study

2019nCoV-415 and Study 2019nCoV-503. During the PBRER reporting interval, no interim analyses were planned or conducted for any of the ongoing clinical trials.

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-315

2019nCoV-315 is a Phase 3, open-label, single arm study to evaluate the safety and immunogenicity of a single dose of a JN.1 subvariant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) recombinant (r) spike (S) protein nanoparticle vaccine (SARS-CoV-2 rS) adjuvanted with Matrix-M™ (NVX-CoV2705) in previously vaccinated adults. Approximately 60 participants will be enrolled to receive a single dose of NVX-CoV2705 on Day 0 and remain on study until Day 28 for immunogenicity with safety data collection up to 180 days post-vaccination. No interim analysis for this study was planned or conducted during the reporting interval for this PBRER.

7.2.3 Study 2019nCoV-415

Study 2019nCoV-415 is a prospective interventional study conducted at the University of Utah Health to assess the impact of reactogenicity among health care workers and first responders receiving an updated 2024-25 Novavax COVID-19 vaccine (NVX-CoV2705) as compared with those receiving a 2024-25 Pfizer-BioNTech mRNA COVID-19 vaccine (Comirnaty) in a real-world setting in the US. No interim analysis was conducted during the reporting interval for this PBRER.

7.2.4 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 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, Nuvaxovid XBB.1.5 or Nuvaxovid JN.1 were ongoing during the reporting interval.

7.5 New Safety Data Related to Fixed Combination Therapies

During the reporting interval, there was 1 ongoing NVX-sponsored Phase 3 clinical trial, 2019nCoV-CIC-E-301, investigating the CIC vaccine comprising the JN.1-variant adapted COVID-19 vaccine (NVX-CoV-2705) co-formulated with the trivalent nanoparticle influenza hemagglutinin vaccine (tNIV) with Matrix-M™ adjuvant. There were no significant safety findings from the study as of the DLP.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting interval, 3 NVX-sponsored Post-Authorisation Safety Studies (PASS) and 3 NVX-sponsored Post-Authorisation Efficacy Studies (PAES) were ongoing. No NVX-sponsored non-interventional studies were completed during the reporting interval. There was also 1 collaborative research PAES study (BEEHIVE) and 1 collaborative surveillance study (2019nCoV-413) that were 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 8 provides further details of the ongoing 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 3 ongoing and 1 completed investigator-initiated studies. There were no ongoing/completed license partner-sponsored studies during the reporting interval. No significant safety findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported.

Appendix 7, Table 36 summarises details regarding ongoing and completed investigator-initiated studies.

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 13).

Appendix 9 presents interval and cumulative counts of serious and non-serious adverse events of medication errors for all spontaneous, regulatory authority, and literature sources, and serious adverse events from non-interventional studies for each variant.

- Appendix 9A: Medication errors - Nuvaxovid
- Appendix 9B: Medication errors - Nuvaxovid XBB.1.5
- Appendix 9C: Medication errors - Nuvaxovid JN.1

All Individual Case Safety Report (ICSR) data reflect the version valid at the time of the DLP.

9.2.1 Results and Discussion

Cases with Nuvaxovid:

One follow-up ICSR was 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 important medical event [IME] criteria), and 1 death.

Cases with Nuvaxovid XBB.1.5:

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

Cumulatively, 88 ICSRs were retrieved (46 males, 37 females, 5 individuals of unspecified sex, age range 8 – 89 years, when reported). These 88 cumulative ICSRs contained 128 non-serious AEs and no serious AEs. The most frequently reported PTs (n≥10) were Expired product administered (n=39), Product storage error (n=38), and Product administration error (n=28).

Cases with Nuvaxovid JN.1:

Sixty-two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 62 ICSRs were retrieved (46 males, 37 females, 5 individuals of unspecified sex, age range 8 – 89 years, when reported). These 62 cumulative ICSRs contained 70 non-serious AEs and no serious AEs. The most frequently reported PTs (n≥5) were Expired product administered (n=33), Extra dose administered (n=7), Incorrect dose administered (n=6) and Product preparation error (n=5).

During the current reporting interval, a disproportionate number of reports (n=57 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=33 ICSRs). All 33 reports were non-serious with clinical events reported in only 2 cases. Review of associated ICSRs did not demonstrate any concerning cases. 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 PT of 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 4 completed and 19 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 12 provides a summary of non-clinical studies for SARS-CoV-2 rS that were either ongoing or completed during the reporting interval.

Table 12: 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				
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 **(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 safety findings
702-219 Immunogenicity of JN.1, JN.1.13.1, and KP.2 rS in mice **(Complete)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-10/group)	**Immunization Day 0 and 14** 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 safety findings
702-223 Single dose mouse potency study with prototype and JN.1 rS vaccines **(Complete)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n =10/group)	**Immunization Day 0** 3-fold serial dilutions of Prototype and JN.1 DPs (15, 5, 1.67, 0.56, 0.19, 0.06 µg)	No safety findings

Table 12: 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
24#370 Immunogenicity in WT and NLRPS KO mice **(Complete)**	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 safety findings
Ongoing Studies				
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)** 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)** 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 safety findings

Table 12: 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
702-226 Booster Study in Mice Primed with JN.1 rS, XBB.1.5+JN.1 rS, and XBB.1.5+KP.3.1.1 rS **(Ongoing)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n =6 16/group)	**Immunization Day 0 and 14** 1 µg JN.1 rS with 5 µg Matrix-M 1 µg each XBB.1.5 rS+ JN.1 rS with 5 µg Matrix-M 1 µg each XBB.1.5 rS+ KP.3.1.1 rS with 5 µg Matrix-M **Booster – 2.5 month (Day 91)** 1 µg XEC rS, KP.3.1.1 rS or LP.8.1 rS with 5 µg Matrix-M	No safety findings
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 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 safety findings

Table 12: 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
702-194 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 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, XBB.2.3 with 5 µg Matrix-M **Booster (3 month)** 1 µg XBB.1.5 with 5 µg Matrix-M	No safety findings
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 safety findings

Table 12: 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
702-202 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 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 safety findings
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 safety findings

Table 12: 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
702-210 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 safety findings
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 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** 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 safety findings

Table 12: 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
702-222 Booster Study in Mice Primed with JN.1 rS, XBB.1.5+JN.1 rS, and XBB.1.5+KP.3 rS **(In-life complete)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n =6 16/group)	**Immunization Day 0 and 14** 1 µg JN.1 rS with 5 µg Matrix-M 1 µg each XBB.1.5 rS+ JN.1 rS with 5 µg Matrix-M 1 µg each XBB.1.5 rS+ KP.3 rS with 5 µg Matrix-M **Booster - 2 month (Day 77)** 1 µg JN.1 rS, KP.3.1.1 rS or XEC rS with 5 µg Matrix-M	No safety findings
702-224 Immunogenicity of XBB.1.5 DPs in mice **(In-life complete)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n =10/group)	**Immunization Day 0 and 14** 10-fold serial dilutions of XBB.1.5 DPs (0.5, 0.05, 0.005 µg)	No safety findings
702-228 Immunogenicity of JN.1, KP.3.1.1, and XEC 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** 1 µg JN.1 rS with 5 µg Matrix-M 1 µg KP.3.1.1 rS with 5 µg Matrix-M 1 µg XEC rS with 5 µg Matrix-M	No safety findings

Table 12: 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
24-0005 Uptake of Matrix-A and Matrix-C in vivo **(In-life complete)**	SVA Swedish national Veterinary Institute, In life, Novavax, Flowcytometry (Non-GLP)	BALB/c mice mice/group, females, total 80 mice)	Mice were immunized intramuscularly in the right quadriceps femoris (thigh) muscle. At 1, 6, 24, or 48 hours (±15 min) after immunization, the mice are euthanized and the muscle, draining iliac lymph node, and spleen are harvested. Analyzed by flowcytometry. 1. PBS only 2. 2 µg AF647-labeled SARS-CoV-2 rS 3. 2 µg AF647-labeled SARS-CoV-2 rS + Matrix-A 10% BODIPY-labeled. 4. 2 µg AF647-labeled SARS-CoV-2 rS + Matrix-C 10% BODIPY-labeled.	No safety findings
24-0005 ADDENDUM Uptake of Matrix-A and Matrix-C in vivo, ADDENDUM **(In-life complete)**	SVA Swedish national Veterinary Institute, In life, Novavax, Flowcytometry (Non-GLP)	BALB/c mice mice/group, females, total 21 mice)	Mice were immunized intramuscularly in the right quadriceps femoris (thigh) muscle. At 1, 6, 24, or 48 hours (±15 min) after immunization, the mice are euthanized and the muscle, draining iliac lymph node, and spleen are harvested. Analyzed by flowcytometry. 1. PBS only 2. 2 µg AF647-labeled SARS-CoV-2 rS 3. 2 µg AF647-labeled SARS-CoV-2 rS + Matrix-A 10% BODIPY-labeled. 4. 2 µg AF647-labeled SARS-CoV-2 rS + Matrix-C 10% BODIPY-labeled. 5. Naive	No safety findings

Table 12: 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
24-0011 Immunogenicity of deacetylated Fraction-A and Matrix-A using SARS-CoV-2 rS **(In-life complete)**	SVA Swedish national Veterinary Institute, In life, Novavax, Immunogenicity (Non-GLP)	BALB/c mice, (10 mice/group, females, total 130 mice)	Mice were Administered S.C. at the base of the tail on Days 0 and 21. At Day 28 the mice are euthanized, and spleen and blood are harvest. 1. 0.1 µg SARS-CoV-2 rS (BV2373) 2. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Matrix-A intact. 3. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Matrix-A 50% deacetylated. 4. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Matrix-A 75% deacetylated. 5. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Matrix-A 100% deacetylated. 6. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Fraction-A intact. 7. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Fraction-A 50% deacetylated. 8. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Fraction-A 75% deacetylated. 9. 0.1 µg SARS-CoV-2 rS (BV2373) + 10 µg Fraction-A 100% deacetylated. 10. 0.1 µg SARS-CoV-2 rS (BV2373) + 2.5 µg Matrix-A intact. 11. 0.1 µg SARS-CoV-2 rS (BV2373) + 2.5 µg Matrix-A 50% deacetylated. 12. 0.1 µg SARS-CoV-2 rS (BV2373) + 2.5 µg Matrix-A 75% deacetylated. 13. 0.1 µg SARS-CoV-2 rS (BV2373) + 2.5 µg Matrix-A 100% deacetylated.	No safety findings

Table 12: 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

Abbreviations: 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 85 publications were retrieved, of which 5 publications summarized below presented new or significant findings on safety (n=4) or safety and immunogenicity (n=1). Six publications presented new or significant findings regarding efficacy (n=1), effectiveness (n=4), or efficacy and immunogenicity (n=1) and are summarized in Section 17.2. All citations are presented in Appendix 22.

Review of the 5 publications did not identify any new safety findings that impact the overall benefit-risk balance of Nuvaxovid vaccines.

"Local and systemic reactogenicity after mRNA and protein-based COVID-19 vaccines compared to meningococcal vaccine (MenACWY) in a UK blinded, randomized phase 2 trial (COV-BOOST)" presented results from COV-BOOST which is a multicenter, blinded, randomized, phase 2 clinical trial , to assess the safety, reactogenicity, and immunogenicity of homologous and heterologous COVID-19 boosters compared to a routinely used vaccine, the meningococcal conjugate vaccine (MenACWY) in ≥30-year-old UK adults. Adult participants received a third COVID-19 vaccine dose (NVX-CoV2373, BNT162b2, or mRNA1273) in addition to MenACWY as an active control. The occurrence of solicited reactogenicity events following the third vaccination was recorded daily in participants' electronic diaries for 7 days. The percentage of participants who reported local events (pain, warmth, redness, itch, swelling, and/or hardness) and systemic events (malaise, muscle ache, fatigue, headache, joint pain, fever, feverishness, diarrhea, and/or nausea) after vaccination were measured. Feverishness was defined as feeling unwell/shivery but not always associated with measurable fever. Grade 3 events were considered severe and Grade 4 events were considered to be potentially life-threatening. The difference in percentage of events following COVID-19 vaccination compared to the percentage of events following MenACWY vaccination with 95% confidence intervals (CI) were calculated. The authors reported that mRNA vaccines, particularly mRNA1273, showed the greatest relative increase in side effects, while NVX-CoV2373 elicited similar reactogenicity to MenACWY. [Marchese 2024]

"The Platform Trial In COVID-19 Priming and BOOsting (PICOBOO): the immunogenicity, reactogenicity, and safety of different COVID-19 vaccinations administered as a second booster (fourth COVID-19 vaccine dose) in AZD1222 primed individuals aged 50 – <70 years old" reported results from PICOBOO, which is a randomised, adaptive trial evaluating the immunogenicity, reactogenicity, and safety of COVID-19 booster strategies in Australia. The authors reported data for second boosters among individuals 50 – < 70 years old primed with AZD1222 (5 – < 70y-AZD1222) until Day 84. AZD1222, the Oxford–AstraZeneca COVID-19 vaccine sold as brand names Covishield and Vaxzervria, is a viral vector vaccine for the prevention of COVID-19. Immunocompetent adults who received any first booster ≥ three months prior were eligible. Participants were randomly allocated to

BNT162b2, mRNA-1273 or NVX-CoV2373 1:1:1. Limited neutralisation against Omicron subvariants was found following all vaccines. Severe reactogenicity events were < 4%. The authors concluded that all vaccines were immunogenic with more rapid waning after mRNA vaccines. These data support boosting with vaccines with greater specificity for circulating Omicron subvariants. [McLeod 2024]

"Association of new onset seizure and COVID-19 vaccines and long-term follow-up: A systematic review and meta-analysis" reported a systematic search to investigate seizure occurrence among COVID-19 vaccine recipients compared to unvaccinated controls. Forty studies were included in the qualitative synthesis and seven of the 40 studies were included in the meta-analysis. Only one study included individuals who received Nuvaxovid. There was no statistically significant difference in the risk of new onset seizure incidence between COVID-19 vaccinated individuals and unvaccinated individuals. [Rafati 2024]

"Short-Term Active Safety Surveillance of the Spikevax and Nuvaxovid Priming Doses in Australia" reported results from the authors' study of the short-term safety profile of primary series doses of the Spikevax and Nuvaxovid vaccines administered between September 2021 and September 2023. Australia began administration of Spikevax (Moderna mRNA-1273) COVID19 vaccine in Aug-2021 and Nuvaxovid (Novavax NVX-CoV2373) in Jan-2022. Online surveys were sent via AusVaxSafety, Australia's active vaccine safety surveillance system, three and eight days after vaccination. A total of 131,775 day 3 surveys were sent, with a response rate of 38.5% (N = 50,721). A total of 43,875 day 8 surveys matched with day 3 survey responses were sent, with a response rate of 71.5% (N = 31,355). Half (50.7%) of respondents reported adverse events following immunisation (AEFI) in 0 – 3 days after vaccination and 24.6% reported AEFI 4–7 days after vaccination. Fatigue, local pain, headache, and myalgia were the most frequently reported symptoms for both vaccines in both periods. After adjusting for respondent characteristics, vaccination clinic type, jurisdiction, and medical conditions, the odds for reporting AEFI increased with age from 16 – 19 years to highest odds at 30–39 years, after which it declined. Females had greater odds of reporting AEFIs than males across most age groups, vaccine types, and doses. Respondents with a history of anaphylaxis had greater odds of reporting any AEFI (adjusted OR range: 1.50 – 2.86). A total of 3.1% of respondents reported seeking medical review 0 – 3 days after vaccination. This study affirms the short-term safety of Spikevax and Nuvaxovid COVID-19 vaccine primary series doses in a large sample in Australia. [Reynolds 2024]

"Risk for Facial Palsy after COVID-19 Vaccination, South Korea, 2021-2022" presented results from the authors' self-controlled case series study to investigate the association between COVID-19 vaccination and facial palsy in South Korea. The study used a large immunization registry linked with the national health information database and included 44,564,345 patients ≥18 years of age who received ≥1 dose of COVID-19 vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, or Ad.26.COV2.S) and had a facial palsy diagnosis and corticosteroid prescription within 240 days postvaccination. The authors compared facial palsy incidence in a risk window of days 1–28 with a control window (the remainder of the 240-day observation period, excluding any risk windows). They found

5,211 patients experienced facial palsy within the risk window, corresponding to 4.0 facial palsy cases/1 million doses, and 10,531 experienced facial palsy within the control window. Facial palsy risk increased within 28 days post-vaccination, primarily after first and second doses and was observed for both mRNA and viral vaccines. No cases of facial palsy were reported after Nuvaxovid vaccination. [Yoon 2024]

12 OTHER PERIODIC REPORTS

Periodic reports submitted to relevant health authorities during the reporting interval by SIIPL (Covovax) and NVX (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) are listed in Table 13 below.

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

Table 13: Periodic Summary Safety Reports Submitted to Health Authorities

Periodic Report	Reporting Interval	Submission Countries
Covovax PSUR No.04	16-Feb-2024 to 15-Aug-2024	South Africa
Nuvaxovid SSR No.30	01-Jun-2024 to 30-Jun-2024	US
Nuvaxovid SSR No.31	01-Jul-2024 to 31-Jul-2024	US
Nuvaxovid SSR No.32	01-Aug-2024 to 31-Oct-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

No new signals were validated during the current reporting interval.

A cumulative tabulation of all new, ongoing or closed signals are presented in Appendix 6, 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
- Acute Kidney Injury
- Acute Liver Injury
- Anaphylaxis
- Autoimmune Hepatitis
- Autoimmune Thyroiditis
- Bell's Palsy
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Fibromyalgia
- Foetal Growth Restriction
- Generalised Convulsions
- Gestational Diabetes
- Guillain-Barré Syndrome
- Haemorrhagic Stroke
- Ischaemic Stroke
- Kawasaki's Disease
- 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
- Pre-eclampsia
- Preterm Birth
- Rheumatoid Arthritis
- Spontaneous Abortion
- Stillbirth
- Sudden Death
- Thrombocytopenia

- Major Congenital Anomalies
- Maternal Death
- Microcephaly
- Multiple Sclerosis
- 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 the variant adapted formulations (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1). Numerator data are derived from AESI search strategies (Appendix 12). Denominator data are derived from actual and estimated exposure for all formulations combined and individually. 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 11 for a complete view of O/E tables), with the exception of anaphylaxis for which O/E analysis is performed on both unadjudicated and adjudicated cases pursuant to a request from the European Medicines Agency (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 numerator counts used for O/E may be lower than AESI ICSR counts used in other parts of the document.

Time-to-onset (TTO) of an AESI is calculated at the individual case level, as described in Section 11.6 of Appendix 10 and may differ from TTO presented in other parts of this document. Risk windows are applied according to published recommendations, and in instances where 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 10 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 windows, background incidence rates, administration data, and calculations used for the analyses are presented in Appendix 10.

Overview of AESI Results

The global vaccine safety database was queried for interval and cumulative ICSRs for all AESIs using the pre-specified search strategies in Appendix 12. Cumulative O/E analyses were performed up to the DLP of 19-Dec-2024.

No ICSRs were reported for the following 9 AESIs for any Novavax COVID-19 vaccine formulation according to prespecified O/E search strategies:

- Acute Disseminated Encephalomyelitis
- Foetal Growth Restriction
- Gestational Diabetes
- Kawasaki's Disease
- Maternal Death
- Microcephaly
- Narcolepsy
- Neonatal Death
- Stillbirth

In addition to the 9 AESIs for which no ICSRs have been reported for all vaccines combined, an additional 2 AESIs have no associated ICSRs for Nuvaxovid:

- Major Congenital Anomalies
- Oculomotor Cranial Nerve Disorder

In addition to the 9 AESIs for which no ICSRs have been reported for all NVX COVID-19 vaccines combined, an additional 17 AESIs have no associated ICSRs for Nuvaxovid XBB.1.5:

- Acute Kidney Injury
- Acute Liver Injury
- Anaphylaxis
- Autoimmune Hepatitis
- Autoimmune Thyroiditis
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Guillain-Barré Syndrome
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Myasthenia Gravis
- Myocardial Infarction
- Optic Neuritis
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Vaccine Associated Enhanced Disease

In addition to the 9 AESIs for which no ICSRs have been reported for all NVX COVID-19 vaccines combined, an additional 26 AESIs have no associated ICSRs for Nuvaxovid JN.1:

- Acute Kidney Injury
- Acute Liver Injury
- Autoimmune Hepatitis
- Autoimmune Thyroiditis
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Fibromyalgia
- Guillain-Barré Syndrome
- Major Congenital Anomalies
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Myasthenia Gravis
- Oculomotor Cranial Nerve Disorders
- Optic Neuritis
- Postural Orthostatic Tachycardia Syndrome
- Pre-eclampsia
- Preterm birth
- Rheumatoid arthritis
- Spontaneous abortion
- Sudden death
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Transverse myelitis
- Vaccine Associated Enhanced Disease
- Venous thromboembolism

During the reporting interval, no new AESI signals were validated and no new AESI crossed the threshold for statistical significance for the overall estimate. No significant changes in O/E were detected for any AESI.

O/E results are summarized with each AESI, and full O/E tables are included in Appendix 11.

Note: In the outputs in Appendix 11, O/E results for all Novavax COVID-19 vaccines are included under "Novavax COVID-19 Vaccines," O/E results for Nuvaxovid are included under "Novavax COVID-19 Vaccine, Adjuvanted," O/E results for Nuvaxovid XBB.1.5 are included under "Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)" and O/E results for Nuvaxovid JN.1 are included under "Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 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 12).

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.

Cases with Nuvaxovid JN.1:

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 Acute Kidney Injury

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for acute kidney injury (refer to Appendix 12).

15.2.2.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (3 females, age range 38 – 41 years, when reported). The 3 cumulative ICSRs included 3 AEs coded to PTs: Acute Kidney Injury (n=2) and Renal Failure (n=1). All the 3 AEs were serious, with the events meeting the medically significant (based on medical judgement or serious by convention, meeting IME criteria) seriousness criteria.

Cases with Nuvaxovid XBB.1.5:

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

Cases with Nuvaxovid JN.1:

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-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO for 1 of 3 AEs was reported as 4 days, which fell within the risk window of 0 – 42 days (refer to Table 39). The TTO were not reported for the other 2 AEs, which were conservatively included in the O/E analyses. Therefore, all 3 AEs met the inclusion criteria for the observed count (n=3). 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 Nuvaxovid JN.1. The observed rate was lower than expected for Nuvaxovid.

15.2.2.3 Conclusion

Three ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines and Nuvaxovid analyses.

No safety signal was identified.

15.2.3 Acute Liver Injury

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for acute liver injury (refer to Appendix 12).

15.2.3.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (1 male, 4 females, age range 38 – 69 years). The 5 cumulative ICSRs included 6 AEs coded to PTs: Liver injury (n=3), Autoimmune hepatitis (n=2), and Drug-induced liver injury (n=1). All 6 AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criteria): 6 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 3 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

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

Cases with Nuvaxovid JN.1:

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

15.2.3.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO for 2 of 5 ICSRs were 14 days and 25 days respectively, which fell within the risk window of 0 – 42 days (refer to Table 39). The TTOs were not reported for 2 ICSRs and these ICSRs were conservatively included in the O/E analyses. TTO for the remaining ICSR was reported as 92 days, which fell outside the risk window. Therefore, 4 ICSRs met the inclusion criteria for the observed count (n=4). 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 Nuvaxovid JN.1. The observed rate was lower than expected for Nuvaxovid.

15.2.3.3 Conclusion

Four ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines and Nuvaxovid analyses.

No safety signal was identified.

15.2.4 Anaphylaxis

A signal of anaphylaxis was validated on 18-May-2022, following a request for a label update from Therapeutic Goods Administration (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.

15.2.4.1 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 12).

Cases with Nuvaxovid:

Three follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 75 ICSRs were retrieved (13 males, 62 females, age range 17 – 75 years, when reported). The 75 cumulative ICSRs included 87 AEs coded to PTs: Anaphylactic reaction (n=48), Anaphylactoid reaction (n=24), Anaphylactic shock (n=7), Circulatory collapse (n=6), Shock (n=1), and Type I hypersensitivity (n=1). All the 87 AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 87 medically significant (based on medical judgement or serious by convention, meeting IME 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.

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, age range 45-82 years). The 2 cumulative ICSRs included 2 AEs coded to PT: Anaphylactic reaction (n=2). All the 2 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.

15.2.4.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 39).

Refer to Table 14 for a summary of AEs included in the O/E analyses. Results of O/E with sensitivity analysis are presented in Table 15. In addition, cumulative O/E analysis stratified by age and sex is presented in Table 16. O/E was also performed for adjudicated cases and results are presented in Table 17.

Table 14: AEs Included in O/E Analysis for Anaphylaxis

Parameters	Unadjudicated				Adjudicated			
	All Vaccines	**Nuvaxovid**	**Nuvaxovid XBB.1.5**	**Nuvaxovid JN.1**	**All Vaccines**	**Nuvaxovid**	**Nuvaxovid XBB.1.5**	**Nuvaxovid JN.1**
Total ICSRs	77	75	0	2	14	14	0	0
Total AEs included in O/E analysis	77	75	0	2	14	14	0	0
Number of AEs with TTO reported	69	67	Not Applicable	2	14	14	Not Applicable	Not Applicable
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	8	8	Not Applicable	0	0	0	Not Applicable	Not Applicable
AEs with TTO falling outside risk windows (All AEs)								
Risk window 0 – 1 day	6	6	Not Applicable	0	0	0	Not Applicable	Not Applicable
Risk window 0 – 2 days	4	4	Not Applicable	0	0	0	Not Applicable	Not Applicable
Risk window 0 – 7 days	3	3	Not Applicable	0	0	0	Not Applicable	Not Applicable
Total AEs included in O/E analysis (all AEs) stratified by risk window								
Risk window 0 – 1 day	71	69	Not Applicable	2	14	14	Not Applicable	Not Applicable
Risk window 0 – 2 days	73	71	Not Applicable	2	14	14	Not Applicable	Not Applicable
Risk window 0 – 7 days	74	72	Not Applicable	2	14	14	Not Applicable	Not Applicable

Table 14: AEs Included in O/E Analysis for Anaphylaxis

Parameters	Unadjudicated				Adjudicated			
	All Vaccines	**Nuvaxovid**	**Nuvaxovid XBB.1.5**	**Nuvaxovid JN.1**	**All Vaccines**	**Nuvaxovid**	**Nuvaxovid XBB.1.5**	**Nuvaxovid JN.1**
Total AEs included in O/E age and gender stratified analysis (all AEs)								
Risk window 0 – 7 days	74	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

Risk window 0 – 1 day: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 day (n=71) for the All-NVX-COVID-19 Vaccines O/E analysis, the unadjudicated observed rate was significantly greater than expected with a rate ratio (RR) of 9.41 (95% CI: 7.35 – 11.87). When assessing by vaccine formulation, the unadjudicated observed rate for Nuvaxovid (n=69) was significantly greater than expected with an RR of 14.71 (95% CI: 11.44 – 18.61). The unadjudicated observed rate was non-significantly greater than expected for Nuvaxovid JN.1 (n=2). No cases were reported for Nuvaxovid XBB.1.5.

Risk window 0 – 2 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=73) for the All-NVX-COVID-19 Vaccines O/E analysis, the unadjudicated observed rate was significantly greater than expected with an RR of 4.83 (95% CI: 3.79 – 6.08). When assessing by vaccine formulation, the unadjudicated observed rate for Nuvaxovid (n=71) was significantly greater than expected with an RR of 7.56 (95% CI: 5.90 – 9.53). The unadjudicated observed rate was non-significantly greater than expected for Nuvaxovid JN.1 (n=2). No cases were reported for Nuvaxovid XBB.1.5.

Risk window 0 – 7 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=74) for the All-NVX-COVID-19 Vaccines O/E analysis, the unadjudicated observed rate was significantly greater than expected with an RR of 1.40 (95% CI: 1.10 – 1.76). When assessing by vaccine formulation, the unadjudicated observed rate for Nuvaxovid (n=72) was significantly greater than expected with an RR of 2.19 (95% CI: 1.71 – 2.76). The unadjudicated observed rate was lower than expected for Nuvaxovid JN.1 (n=2). No cases were reported for Nuvaxovid XBB.1.5.

Table 15: 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	9.41 (7.35 – 11.87) [1]	18.83 (15.86 – 22.12) [1]	37.65 (33.40 – 42.23) [1]
0 – 2 Days	4.83 (3.79 – 6.08) [1]	9.67 (8.16 – 11.33) [1]	19.33 (17.18 – 21.65) [1]
0 – 7 Days	1.40 (1.10 – 1.76) [1]	2.80 (2.37 – 3.28) [1]	5.60 (4.98 – 6.27) [1]
Nuvaxovid			
0 – 1 Day	14.71 (11.44 – 18.61) [1]	29.41 (24.71 – 34.63) [1]	58.82 (52.09 – 66.07) [1]
0 – 2 Days	7.56 (5.90 – 9.53) [1]	15.11 (12.73 – 17.76) [1]	30.23 (26.81 – 33.90) [1]
0 – 7 Days	2.19 (1.71 – 2.76) [1]	4.38 (3.69 – 5.14) [1]	8.76 (7.78 – 9.82) [1]
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

Table 15: 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
Nuvaxovid JN.1			
0 – 1 Day	2.02 (0.24 – 7.28)	4.03 (1.10 – 9.59) [1]	8.07 (3.48 – 15.23) [1]
0 – 2 Days	1.01 (0.12 – 3.64)	2.02 (0.55 – 4.79)	4.03 (1.74 – 7.61) [1]
0 – 7 Days	0.29 (0.03 – 1.04)	0.58 (0.16 – 1.37)	1.15 (0.50 – 2.18)

[1] Observed rates significantly greater than expected.

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

The results of unadjudicated O/E analyses for anaphylaxis with a 7-Day risk window, stratified by age and sex, are presented in Table 16 below. When accounting for all cumulative anaphylaxis reports meeting inclusion criteria (n=74) 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 5.02 (95% CI: 2.60 – 8.78). Unadjudicated observed rates were significantly greater than expected in the 40 – 49-year-old male group (n=3) with an RR of 7.23 (95% CI: 1.49 – 21.13). The unadjudicated observed rate as reported in the total female group (n=62) was significantly greater than expected with an RR of 10.44 (95% CI: 8.00 – 13.38). Unadjudicated observed rates were significantly greater than expected in the 0 – 19-year-old female group (n=5) with an RR of 42.53 (95% CI: 13.78 – 99.26), in the 20 – 29-year-old female group (n=4) with an RR of 6.55 (95% CI: 1.79 – 16.77), in the 30 – 39-year-old female group (n=15) with an RR of 12.38 (95% CI: 6.93 – 20.42), in the 40 – 49-year-old female group (n=21) with an RR of 15.40 (95% CI: 9.54 – 23.55), in the 50 – 59-year-old female group (n=12) with an RR of 9.39 (95% CI: 4.85 – 16.39), and in the 60 – 69-year-old female group (n=4) with an RR of 4.62 (95% CI: 1.26 – 11.83).

Table 16: Unadjudicated O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Sex (Risk Window 0 – 7 Days)

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 – 18.25)	5	42.53 (13.78 – 99.26) [1]
20 – 29	2	8.33 (1.00 – 30.07)	4	6.55 (1.79 – 16.77) [1]
30 – 39	2	5.75 (0.69 – 20.75)	15	12.38 (6.93 – 20.42) [1]
40 – 49	3	7.23 (1.49 – 21.13) [1]	21	15.40 (9.54 – 23.55) [1]
50 – 59	1	2.27 (0.07 – 12.63)	12	9.39 (4.85 – 16.39) [1]
60 – 69	1	2.30 (0.07 – 12.79)	4	4.62 (1.26 – 11.83) [1]
70 – 79	0	0 (0 – 14.86)	0	0 (0 – 9.74)

Table 16: Unadjudicated O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Sex (Risk Window 0 – 7 Days)

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Doses				
80+	0	0 (0 – 68.83)	1	8.69 (0.26 – 48.42)
Missing	3	Not Applicable	0	Not Applicable
Total	12	5.02 (2.60 – 8.78) [1]	62	10.44 (8.00 – 13.38) [1]

[1] Observed rates significantly greater than expected.

15.2.4.3 Results of O/E Analysis following Adjudication (Overall Dose Series)

Of the 75 ICSRs retrieved by the AESI search strategy for anaphylaxis and subsequently adjudicated against the established Brighton Collaboration case definition for Anaphylaxis, 14 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 39). A TTO of 0 was reported for all 14 adjudicated cases and therefore all cases (n=14) were included in the analyses for all risk windows. An All-NVX-COVID-19 Vaccines O/E analysis for adjudicated cases was performed in addition to formulation-specific O/E analyses.

Refer to Table 17 for O/E results following adjudication, for Brighton Collaboration Level 1 – 3 anaphylaxis cases.

Table 17: 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	1.86 (1.01 – 3.11) [1]
0 – 2 Days	0.93 (0.51 – 1.56)
0 – 7 Days	0.26 (0.14 – 0.44) [2]
Nuvaxovid	
0 – 1 Day	2.98 (1.63-5.01) [1]
0 – 2 Days	1.49 (0.81-2.50)
0 – 7 Days	0.43 (0.23 – 0.71) [2]
Nuvaxovid XBB.1.5	
0 – 1 Day	Not Applicable
0 – 2 Days	Not Applicable
0 – 7 Days	Not Applicable

Table 17: O/E Analysis (Brighton Collaboration Levels 1-3) following Adjudication – All Cumulative adjudicated AEs

Risk Window	O/E Rate Ratio (95 % CI)
Nuvaxovid JN.1	
0 – 1 Day	Not Applicable
0 – 2 Days	Not Applicable
0 – 7 Days	Not Applicable

[1] Observed rates significantly greater than expected.

[2] Observed rates significantly lower than expected.

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=14) for the All-NVX-COVID-19 Vaccines O/E analysis, the observed rate was significantly greater than expected with an RR of 1.86 (95% CI: 1.01 – 3.11). When assessing by vaccine formulation, the adjudicated observed rate for Nuvaxovid (n=14) was significantly greater than expected with an RR of 2.98 (95% CI: 1.63 – 5.01). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

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=14) for the All-NVX-COVID-19 Vaccines O/E analysis, the observed rate was lower than expected. When assessing by vaccine formulation, the adjudicated observed rate for Nuvaxovid (n=14) was non-significantly greater than expected. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

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=14) for the All-NVX-COVID-19 Vaccines O/E analysis, the observed rate was lower than expected. When assessing by vaccine formulation, the adjudicated observed rate for Nuvaxovid (n=14) was lower than expected. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.4.4 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.

15.2.4.5 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 10.

15.2.4.6 Conclusion

A total of 77 ICSRs were reported cumulatively. There were 74 AEs that met inclusion criteria for the unadjudicated observed count for the All-NVX-COVID-19 Vaccines O/E analyses for the 0 – 7 days risk window. The unadjudicated observed rate was significantly greater than expected for All-NVX-COVID-19 Vaccines and when assessing by vaccine formulation for Nuvaxovid. For Nuvaxovid JN.1 the observed rate was lower than expected. No AEs have been reported for Nuvaxovid XBB.1.5. Observed rates were also significantly greater than expected for the 0 – 1 and 0 – 2 day risk windows for All-NVX-COVID-19 Vaccines and when assessing by vaccine formulation for Nuvaxovid. For Nuvaxovid JN.1 the observed rate was non-significantly greater than expected for the 0 – 1 day and 0 – 2 day risk windows. Observed rates, stratified by age and sex, were significantly greater than expected for the total male group, males 40 – 49 years, females 0 – 69 years, and the total female group.

A total of 14 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-NVX-COVID-19 Vaccines and when assessing by vaccine formulation for Nuvaxovid, the observed rates were significantly greater than expected for the 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.

15.2.5 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 12)

15.2.5.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.5.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 VaccinesO/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 39). The TTO was not reported for the other AE, which 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, the observed rate was lower than expected for Nuvaxovid. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.5.3 Conclusion

One ICSR met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines and Nuvaxovid analyses.

No safety signal was identified.

15.2.6 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 12).

15.2.6.1 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.

Cases with Nuvaxovid JN.1:

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-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO were 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 39). O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, the observed rate was lower than expected for Nuvaxovid. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.6.3 Conclusion

Three ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines and Nuvaxovid analyses.

No safety signal was identified.

15.2.7 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 12).

15.2.7.1 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:

No 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.

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, age [redacted]). The ICSR included 1 AE coded to PT: Facial paralysis. The reported AE was serious, due to medical significance of the event (based on medical judgement or serious by convention, meeting IME criteria).

15.2.7.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO for 23 of 26 ICSRs ranged from 0 – 25 days, which were within the risk window of 0 – 42 days (refer to Table 39). TTO were not reported for the other 3 AEs and these AEs were conservatively included in the O/E analyses. Therefore 26 AEs met inclusion criteria for the observed count (n=26). O/E and sensitivity analyses showed that the All-NVX-COVID-19 Vaccines unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=24), Nuvaxovid XBB.1.5 (n=1) and Nuvaxovid JN.1 (n=1).

15.2.7.3 Conclusion

Twenty-six AEs met TTO inclusion criteria and results of the O/E and sensitivity analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines, Nuvaxovid, Nuvaxovid XBB.1.5. and Nuvaxovid JN.1.

No safety signal was identified.

15.2.8 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 12).

15.2.8.1 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 15.2.42).

Cases with Nuvaxovid XBB.1.5:

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

Cases with Nuvaxovid JN.1:

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-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39) and met inclusion criteria for the observed count (n=1). Unadjudicated O/E showed that the observed rate was lower than expected. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.8.3 Conclusion

The single ICSR met TTO inclusion criteria and O/E analysis showed the observed rate was lower than expected.

No safety signal was identified.

15.2.9 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 12).

15.2.9.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.9.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). 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, the unadjudicated observed rate was lower than expected for Nuvaxovid. No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.9.3 Conclusion

Two AEs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid vaccine analyses.

No safety signal was identified.

15.2.10 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 12).

15.2.10.1 Results and Discussion

Cases with Nuvaxovid:

No 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.

Cases with Nuvaxovid JN.1:

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

15.2.10.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). The TTO were 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, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=5). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.10.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines and Nuvaxovid analyses.

No safety signal was identified.

15.2.11 Fibromyalgia

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for fibromyalgia (refer to Appendix 12).

15.2.11.1 Results and Discussion

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (1 male, 4 females, age range 49 – 64 years, when reported). The 5 cumulative ICSRs included 5 AEs coded to the PT Fibromyalgia (n=5). Of 5 reported AEs, 1 AE was serious due to medical significance of the event (based on medical judgement).

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).

Cases with Nuvaxovid JN.1:

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

15.2.11.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO for 3 of 6 AEs ranged from 0 – 22 days, which were within the risk window of 0 – 42 days (refer to Table 39). The TTO were 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=6). O/E and sensitivity analyses results showed the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was

lower than the expected for both Nuvaxovid (n=5) and Nuvaxovid XBB.1.5 (n=1). No cases were reported for Nuvaxovid JN.1.

15.2.11.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid XBB.1.5 vaccine analyses.

No safety signal was identified.

15.2.12 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 12).

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.

Cases with Nuvaxovid JN.1:

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

15.2.12.2 Conclusion

No safety signal was identified.

15.2.13 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 12).

15.2.13.1 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:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (1 male, 3 females, age range 31 – 72 years) and included 4 serious AEs coded to PT: Seizure (n=4), with the events meeting the medically significant (based on medical judgement or serious by convention, meeting IME criteria) seriousness criterion.

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, ages 29 and 31 years). The 2 cumulative ICSRs included 2 serious AEs coded to PTs: Seizure (n=2) with the events meeting the medically significant (based on medical judgement or serious by convention, meeting IME criteria) seriousness criterion.

15.2.13.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 39).

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO for 15 AEs were reported and ranged between 0 – 6 days, which fell within the risk window (0 – 7 days). The TTO were not reported for 2 AEs, and both were conservatively included in the O/E analyses. 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. Therefore, seventeen AEs met the inclusion criteria for the observed count (n=17) 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=14) for the All-NVX-COVID-19 Vaccines 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 2.84 (95% CI: 2.14 – 3.66). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected when assuming 75% underreporting for Nuvaxovid (n=8) with an RR of 2.20 (95% CI: 1.50 – 3.06) and Nuvaxovid XBB.1.5 (n=4) with an RR of 3.75 (95% CI: 2.14 – 5.94). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid JN.1 (n=2) when assuming 50% underreporting with an RR of 4.29 (1.17 – 10.20) and 75% underreporting with an RR of 8.58 (95% CI: 3.70 – 16.19).

Additional risk windows: For the All-NVX-COVID-19 Vaccines 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=17) and 0 – 2 days (n=15) and each showed that the overall unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid and Nuvaxovid XBB.1.5. For Nuvaxovid JN.1 the overall unadjudicated observed rate was lower than the expected rate for the 0 – 7 day risk window and non-significantly greater than expected for the 0 – 2 day risk window.

O/E results based on multiple risk windows for generalised convulsions are included in Appendix 11.

15.2.13.3 Conclusion

Seventeen AEs met inclusion criteria for the All-NVX-COVID-19 Vaccines O/E analyses for the 0 – 7 day risk window. O/E analyses 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 analyses conducted using a risk window of 0 – 1 days showed the unadjudicated observed rate was significantly greater than expected at 75% sensitivity for All-NVX-COVID-19 Vaccines, Nuvaxovid, and Nuvaxovid XBB.1.5, and at 50% for Nuvaxovid JN.1.

No safety signal was identified.

15.2.14 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 12).

15.2.14.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.14.2 Conclusion

No safety signal was identified.

15.2.15 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 12).

15.2.15.1 Results and Discussion

Cases with Nuvaxovid:

Two follow-ups have been retrieved for the current reporting interval.

Cumulatively, 10 ICSRs were retrieved (6 males, 3 females, 1 individual of unspecified gender, 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.

Cases with Nuvaxovid JN.1:

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

15.2.15.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). 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). For All-NVX-COVID-19 Vaccines, the unadjudicated observed rate was lower than the expected rate; however, the unadjudicated observed rate was non-significantly greater than expected at 50% underreporting and was significantly greater than expected when assuming 75% underreporting with an RR of 2.82 (95% CI: 1.93 – 3.92). When assessing by vaccine formulation, the unadjudicated observed rate was greater than expected for Nuvaxovid (n=8), but this was not statistically significant unless assuming 50% underreporting with an RR of 2.32 (95% CI: 1.33 – 3.68) or 75% underreporting with an RR of 4.65 (95% CI: 3.18 – 6.48). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.15.3 Conclusion

Eight ICSRs met TTO inclusion criteria for O/E analyses. For All-NVX-COVID-19 Vaccines, while the unadjudicated observed rate was non-significantly greater than the expected rate at 50% underreporting, it became significantly greater than expected when assuming 75% underreporting. For Nuvaxovid, the unadjudicated observed rate became significantly greater than expected at 50% underreporting.

No safety signal was identified.

15.2.16 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 12).

15.2.16.1 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.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (unknown age and gender). The ICSR included 1 serious AE coded to PT: Cerebrovascular accident with the event meeting the following criteria:

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

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (76 years female). The ICSR included 1 serious AE coded to PT: Cerebrovascular accident with the event 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 hospitalisation.

Of note, the same 11 ICSRs were also retrieved by the search strategy for Ischaemic stroke (Section 15.2.17).

15.2.16.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, the TTO for 5 out of 13 AEs ranged from 1 to 10 days which fell within the risk window of 0 – 28 days (refer to Table 39). TTO were not reported for 4 AEs, which were conservatively included in the O/E analysis. The TTO for the remaining 4 AEs ranged from 31 days to 67 days, which fell outside the risk window. Therefore, after excluding 4 AEs falling outside the risk window, a total of 9 AEs met inclusion criteria for the observed count (n=9). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=7), Nuvaxovid XBB.1.5 (n=1) and Nuvaxovid JN.1 (n=1).

15.2.16.3 Conclusion

Nine ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed a lower-than-expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 vaccine analyses.

No safety signal was identified.

15.2.17 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 12).

15.2.17.1 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.

Cases with Nuvaxovid XBB.1.5:

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

Cumulatively, 4 ICSRs were retrieved (1 male, 2 females, 1 individual of unspecified gender, age range 32 – 82 years, when reported). These 4 cumulative ICSRs included 4 AEs coded to PTs: Cerebrovascular accident (n=1), Ischaemic stroke (n=1), Thalamic infarction (n=1), and Transient Ischaemic Attack (n=1). All the 4 AEs were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 4 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid JN.1:

One initial ICSR has been retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (female, aged 76 years). The ICSRs included 1 serious AE coded to PT: Cerebrovascular accident (n=1). The AE was serious, with the event 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 hospitalisation.

Of note, 11 of the 17 ICSRs were also retrieved by the search strategy for Haemorrhagic stroke (Section 15.2.16).

15.2.17.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

The TTO for 13 of 22 AEs ranged from 1 – 21 days, which fell within the risk window of 0 – 28 days (refer to Table 39). TTO were not reported in 5 of the 22 AEs and these AEs were conservatively included in O/E analysis. TTO for the remaining 4 AEs ranged from 31 days to 67 days, which fell outside the risk window. Therefore, after excluding the 4 AEs falling outside the risk window, 18 AEs met inclusion criteria for the observed count (n=18) for O/E analysis. O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than the expected for Nuvaxovid (n=13), Nuvaxovid XBB.1.5 (n=4) and Nuvaxovid JN.1 (n=1).

15.2.17.3 Conclusion

Eighteen ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid, Nuvaxovid XBB.1.5, and Nuvaxovid JN.1 vaccine analyses.

No safety signal was identified.

15.2.18 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 12).

15.2.18.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.18.2 Conclusion

No safety signal was identified.

15.2.19 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 12).

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:

One initial ICSR has been retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 male foetus). The ICSR included 2 AEs coded to PTs: Ventricular septal defect (n=1) and Congenital aortic valve stenosis (n=1). Both 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 2 congenital anomaly/birth defect.

Cases with Nuvaxovid JN.1:

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

15.2.19.2 Conclusion

No safety signal was identified.

15.2.20 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 12).

15.2.20.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.20.2 Conclusion

No safety signal was identified.

15.2.21 Microcephaly

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for microcephaly (refer to Appendix 12).

15.2.21.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.21.2 Conclusion

No safety signal was identified.

15.2.22 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 12).

15.2.22.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.22.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=3). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.22.3 Conclusion

All ICSRs met the TTO inclusion criteria and the results of unadjudicated O/E analyses showed a lower-than-expected rate for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.23 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 12).

15.2.23.1 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.

Cases with Nuvaxovid JN.1:

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-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=1). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.23.3 Conclusion

The single ICSR met TTO inclusion criteria and results of the O/E and sensitivity analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.24 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 12).

15.2.24.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.24.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). The All-NVX-COVID-19 Vaccines O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=1). No cases were reported for Nuvaxovid XBB.1.5 or Nuvaxovid JN.1.

15.2.24.3 Conclusion

A single ICSR met the TTO inclusion criteria. Results of unadjudicated O/E and sensitivity analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.25 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 12).

15.2.25.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were 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.

Cases with Nuvaxovid JN.1:

Five initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (4 males, 1 female, age range 42 – 88 years). The 5 cumulative ICSRs included 5 AEs coded to PTs: Myocardial infarction (n=3) and Troponin increased (n=2). Of the 5 AEs reported, 5 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), 2 hospitalisation, and 3 death.

15.2.25.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO for 10 of 21 AEs ranged from 0 – 14 days, which fell within the risk window of 0 – 28 days (refer to Table 39). Five AEs with TTOs ranging from 60 to 130 days fell outside the risk window and these were excluded from the O/E analysis. TTOs were not reported for the remaining 6 AEs, which were conservatively included in the O/E analyses. Therefore, 16 of 21 AEs met TTO inclusion criteria for the observed count (n=16) for O/E analysis. O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=11) and Nuvaxovid JN.1 (n=5). No cases were reported for Nuvaxovid XBB.1.5.

15.2.25.3 Conclusion

Sixteen AEs met the TTO inclusion criteria. Results of the O/E analyses showed a lower-than-expected rate for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid JN.1.

No safety signal was identified.

15.2.26 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.

15.2.26.1 Myocarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for myocarditis (refer to Appendix 12).

15.2.26.1.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs 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:

No 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.

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (male, 42 years). The 1 cumulative ICSR included 1 AE coded to PT: Myopericarditis. The AE was serious 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 hospitalisation.

15.2.26.1.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 39).

Refer to Table 18 for the stratification of AEs included in unadjudicated O/E analysis.

Table 18: Stratification of AEs Included in Unadjudicated O/E Analysis for Myocarditis

Parameters	Novavax COVID-19 Vaccines, Unadjudicated	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
Total ICSRs	34	31	2	1
Total AEs	34	31	2	1
Number of AEs with TTO reported	19	19	0	1
Number of AEs with TTO missing (conservatively assessed as falling within the risk window)	14	12	2	0
AEs with TTO falling outside risk windows				
Risk window 0 – 7 days	7	7	0	0
Risk window 0 – 14 days	5	5	0	0
Risk window 0 – 30 days	2	2	0	0
Risk window 0 – 42 days	2	2	0	0
Total AEs included in O/E analysis stratified by risk window				
Risk window 0 – 7 days	27	24	2	1
Risk window 0 – 14 days	29	26	2	1
Risk window 0 – 30 days	32	29	2	1
Risk window 0 – 42 days	32	29	2	1
Total AEs included in O/E age and gender stratified analysis				
Risk window 0 – 42 days	32	Not Applicable	Not Applicable	Not Applicable

Risk window 0 – 7 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=27), the unadjudicated observed rate was significantly greater than expected with an RR of 9.15 (95% CI: 6.03 – 13.32). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=24) with an RR of 13.93 (95% CI: 8.93 – 20.73) but non-significantly greater than expected for Nuvaxovid XBB.1.5 (n=2) and Nuvaxovid JN.1 (n=1).

Risk window 0 – 14 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=29), the unadjudicated observed rate was significantly greater than expected with an RR of 4.92 (95% CI: 3.29 – 7.06). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=26) with an RR of 7.55 (95% CI: 4.93 – 11.06) but non-significantly greater than expected for Nuvaxovid XBB.1.5 (n=2) and Nuvaxovid JN.1 (n=1).

Risk window 0 – 30 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=32), the unadjudicated observed rate was significantly greater than expected with an RR of 2.66 (95% CI: 1.82 – 3.76). When assessing by vaccine formulation, unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=29) with an RR of 4.25 (95% CI: 2.85 – 6.11) but lower than expected for Nuvaxovid XBB.1.5 (n=2) and Nuvaxovid JN.1 (n=1).

Risk window 0 – 42 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=32), the unadjudicated observed rate was significantly greater than expected with an RR of 1.97 (95% CI: 1.35 – 2.78). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=29) with an RR of 3.22 (95% CI: 2.15 – 4.62) but lower than expected for Nuvaxovid XBB.1.5 (n=2) and Nuvaxovid JN.1 (n=1).

Table 19: 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	9.15 (6.03 – 13.32) [1]	18.31 (13.76 – 23.70) [1]	36.62 (30.04 – 44.03) [1]
0 – 14 Days	4.92 (3.29 – 7.06) [1]	9.83 (7.46 – 12.61) [1]	19.66 (16.25 – 23.49) [1]
0 – 30 Days	2.66 (1.82 – 3.76) [1]	5.32 (4.10 – 6.75) [1]	10.64 (8.88 – 12.61) [1]
0 – 42 Days	1.97 (1.35 – 2.78) [1]	3.94 (3.04 – 5.00) [1]	7.89 (6.58 – 9.34) [1]
Nuvaxovid			
0 – 7 Days	13.93 (8.93 – 20.73) [1]	27.87 (20.55 – 36.62) [1]	55.74 (45.15 – 67.74) [1]
0 – 14 Days	7.55 (4.93 – 11.06) [1]	15.09 (11.27 – 19.63) [1]	30.18 (24.66– 36.41) [1]
0 – 30 Days	4.25 (2.85 – 6.11) [1]	8.51 (6.46 – 10.92) [1]	17.02 (14.06 – 20.33) [1]
0 – 42 Days	3.22 (2.15 – 4.62) [1]	6.43 (4.89 – 8.25) [1]	12.87 (10.63 – 15.37) [1]
Nuvaxovid XBB.1.5			
0 – 7 Days	2.55 (0.31 – 9.20)	5.10 (1.39– 12.12) [1]	10.20 (4.40 – 19.25) [1]
0 – 14 Days	1.28 (0.15 – 4.60)	2.55 (0.69 – 6.06)	5.10 (2.20 – 9.63) [1]
0 – 30 Days	0.60 (0.07 – 2.15)	1.19 (0.32 – 2.83)	2.38 (1.03 – 4.49) [1]
0 – 42 Days	0.43 (0.05 – 1.53)	0.85 (0.23 – 2.02)	1.70 (0.73 – 3.21)
Nuvaxovid JN.1			
0 – 7 Days	2.26 (0.07 – 12.59)	4.52 (0.54 – 14.51)	9.04 (2.46 – 21.49) [1]
0 – 14 Days	1.13 (0.03 – 6.29)	2.26 (0.27 – 7.25)	4.52 (1.23 – 10.74) [1]
0 – 30 Days	0.54 (0.02 – 3.01)	1.08 (0.13 – 3.47)	2.16 (0.59 – 5.14)
0 – 42 Days	0.40 (0.01 – 2.22)	0.80 (0.10 – 2.56)	1.59 (0.43 – 3.79)

[1] Observed rates significantly greater than expected.

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

When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis AESI reports (n=32), 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=15) was significantly greater than expected with an RR of 1.84 (95% CI: 1.03 – 3.04). The unadjudicated observed rate was significantly greater than expected for the total female group (n=16) with an RR of 2.18 (95% CI: 1.24 – 3.53). This was also the case for the 0 – 19-year-old male group (n=3) with an RR of 18.97 (95% CI: 3.92 – 55.45) and in the 20 – 29-year-old female group (n=6) with an RR of 11.14 (95% CI: 4.08 – 24.25).

Table 20: Unadjudicated O/E Analysis of Myocarditis for All Cumulative Reports Stratified by Age and Sex (Risk Window 0 – 42 Days)

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	18.97 (3.92 – 55.45) [3]	0	0 (0 – 85.73)
20 – 29	2	1.43 (0.17 – 5.17)	6	11.14 (4.08 – 24.25) [3]
30 – 39	3	1.62 (0.33 – 4.73)	1	0.78 (0.02 – 4.33)
40 – 49	4	2.59 (0.71 – 6.64)	3	2.25 (0.46 – 6.57)
50 – 59	1	0.95 (0.03 – 5.28)	3	2.11 (0.44 – 6.17)
60 – 69	0	0 (0 – 3.56)	0	0 (0 – 2.57)
70 – 79	0	0 (0 – 4.76)	1	1.17 (0.04 – 6.54)
80+	1	3.12 (0.09 – 17.37)	0	0 (0 – 8.37)
Missing	1	Not Applicable	2	Not Applicable
Total	15 [1]	1.84 (1.03 – 3.04) [3]	16 [2]	2.18 (1.24 – 3.53) [3]

[1] One AE with TTO of 102 days fell outside all risk windows.

[2] One AE with TTO of 137 days fell outside all risk windows.

[3] Observed rates significantly greater than expected.

15.2.26.1.2.2 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.

15.2.26.1.3 Conclusion

The unadjudicated observed rate was significantly greater than expected among all risk windows for All-NVX-COVID-19 Vaccines and for Nuvaxovid.

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.

15.2.26.2 Pericarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for pericarditis (refer to Appendix 12).

15.2.26.2.1 Results and Discussion

Cases with Nuvaxovid:

No 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 ICSR has been retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (4 males, age range 14 – 76 years). The 4 cumulative ICSRs included 4 AEs coded to PT: Pericarditis (n=4). Of the 4 AEs reported, 3 were serious, with the events meeting the following criteria (an event may meet more than one seriousness

criterion): 4 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 males, age 45 years, when reported). The 2 cumulative ICSRs included 2 AEs coded to PT: Pericarditis (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).

15.2.26.2.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 39 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 21 for stratification of AEs included in O/E analysis.

Table 21: Stratification of AEs Included in Unadjudicated O/E Analysis for Pericarditis

Parameters	Novavax COVID-19 Vaccines unadjudicated	Nuvaxovid	Nuvaxovid XBB 1.5	Nuvaxovid JN.1
Total ICSRs	63	57	4	2
Total AEs	63	57	4	2
Number of AEs with TTO reported	40	36	3	1
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	23	21	1	1
AEs with TTO falling outside risk windows (All AEs)				
Risk window 0 – 7 days	14	12	2	0
Risk window 0 – 14 days	5	4	1	0

Table 21: Stratification of AEs Included in Unadjudicated O/E Analysis for Pericarditis

Risk window 0 – 30 days	2	2	0	0
Risk window 0 – 42 days	1	1	0	0
Total AEs included in O/E analysis (all AEs) stratified by risk window				
Risk window 0 – 7 days	49	45	2	2
Risk window 0 – 14 days	58	53	3	2
Risk window 0 – 30 days	51	55	4	2
Risk window 0 – 42 days	62	56	4	2
Total AEs included in O/E age and gender stratified analysis (all AEs)				
Risk window 0 – 42 days	62	Not Applicable	Not Applicable	Not Applicable

Risk window 0 – 7 days: When accounting for All-NVX-COVID-19 Vaccines cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=49), the unadjudicated observed rate was significantly greater than expected with an RR of 3.16 (95% CI: 2.34 – 4.18). When assessing by vaccine formulation, the observed rate was significantly greater than expected for Nuvaxovid (n=45) with an RR of 4.22 (95% CI: 3.08 – 5.65), but lower than expected for Nuvaxovid XBB.1.5 (n=2). The observed rate was non-significantly greater than expected for Nuvaxovid JN.1 (n=2).

Risk window 0 – 14 days: When accounting for All-NVX-COVID-19 Vaccines cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=58), the unadjudicated observed rate was significantly greater than expected with an RR of 1.87 (95% CI: 1.42 – 2.42). When assessing by vaccine formulation, the observed rate was significantly greater than expected for Nuvaxovid (n=53) with an RR of 2.49 (95% CI: 1.86 – 3.25), but lower than expected for Nuvaxovid XBB.1.5 (n=3). The observed rate was non-significantly greater than expected for Nuvaxovid JN.1 (n=2).

Risk window 0 – 30 days: When accounting for All-NVX-COVID-19 Vaccines cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=61), the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the observed rate was non-significantly greater than expected for Nuvaxovid (n=55) and lower than expected for Nuvaxovid XBB.1.5 (n=3) and Nuvaxovid JN.1 (n=2).

Risk window 0 – 42 days: When accounting for All-NVX-COVID-19 Vaccines cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=62), the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the observed rate was lower than expected for Nuvaxovid (n=56), Nuvaxovid XBB.1.5 (n=4) and Nuvaxovid JN.1 (n=2).

Table 22: 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	3.16 (2.34 – 4.18) [1]	6.33 (5.14 – 7.68) [1]	12.66 (10.95 – 14.52) [1]
0 – 14 Days	1.87 (1.42 – 2.42) [1]	3.74 (3.09 – 4.47) [1]	7.49 (6.56 – 8.50) [1]
0 – 30 Days	0.96 (0.74 – 1.24)	1.93 (1.60 – 2.29) [1]	3.86 (3.39 – 4.36) [1]
0 – 42 Days	0.72 (0.56 – 0.93) [2]	1.45 (1.21 – 1.72) [1]	2.90 (2.55 – 3.28) [1]
Nuvaxovid			
0 – 7 Days	4.22 (3.08 – 5.65) [1]	8.44 (6.79 – 10.33) [1]	16.89 (14.51 – 19.49) [1]
0 – 14 Days	2.49 (1.86 – 3.25) [1]	4.97 (4.07 – 5.99) [1]	9.94 (8.65 – 11.35) [1]
0 – 30 Days	1.29 (0.97 – 1.68)	2.58 (2.12 – 3.09) [1]	5.16 (4.50 – 5.87) [1]
0 – 42 Days	0.98 (0.74 – 1.28)	1.97 (1.62 – 2.36) [1]	3.94 (3.44 – 4.48) [1]
Nuvaxovid XBB.1.5			
0 – 7 Days	0.51 (0.06 – 1.85)	1.03 (0.28 – 2.44)	2.05 (0.88 – 3.87)
0 – 14 Days	0.38 (0.08 – 1.13)	0.77 (0.28 – 1.59)	1.54 (0.80 – 2.61)
0 – 30 Days	0.24 (0.07 – 0.61) [2]	0.48 (0.21 – 0.90) [2]	0.96 (0.55 – 1.52)
0 – 42 Days	0.17 (0.05 – 0.44) [2]	0.34 (0.15 – 0.65) [2]	0.68 (0.39 – 1.08)
Nuvaxovid JN.1			
0 – 7 Days	2.15 (0.26 – 7.77)	4.30 (1.17 – 10.23) [1]	8.61 (3.71 – 16.25) [1]
0 – 14 Days	1.08 (0.1 – 3.88)	2.15 (0.59 – 5.11)	4.30 (1.86 – 8.12) [1]
0 – 30 Days	0.51 (0.06 – 1.86)	1.03 (0.28 – 2.45)	2.06 (0.89 – 3.89)
0 – 42 Days	0.38 (0.05 – 1.37)	0.76 (0.21 – 1.80)	1.52 (0.65 – 2.86)

[1] Observed rates significantly greater than expected.

[2] Observed rates significantly lower than expected.

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

When accounting for All-NVX-COVID-19 Vaccines cumulative pericarditis AESI reports (n=62), 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=33) and the total female group (n=29) was lower than the expected rate.

Table 23: Unadjudicated O/E Analysis of Pericarditis for All Cumulative Reports Stratified by Age and Sex (Risk Window of 0 – 42 Days)

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	3.44 (0.10 – 19.19)	0	0 (0 – 14.62)
20 – 39	15	1.24 (0.70 – 2.05)	12	1.30 (0.67 – 2.28)
40 – 59	11	0.67 (0.33 – 1.19)	12	0.86 (0.44 – 1.50)
60+	2	0.15 (0.02 – 0.54) [1]	5	0.437 (0.12 – 0.86) [1]
Missing	4	Not Applicable	0	Not Applicable
Total	33	0.79 (0.54 – 1.11)	29	0.75 (0.50 – 1.08)

[1] Observed rates significantly lower than expected.

15.2.26.2.2.2 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.

15.2.26.2.3 Conclusion

The unadjudicated O/E analysis showed a significantly greater than expected observed rate for the 0 – 7 and 0 – 14 day risk windows for All-NVX-COVID-19 Vaccines and for Nuvaxovid. Results of the unadjudicated O/E analysis for All-NVX-COVID-19 Vaccines stratified by age and sex were not significantly greater than expected.

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

15.2.26.3 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 12).

15.2.26.3.1 Results and Discussion

Cases with Nuvaxovid:

No 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:

One initial ICSR has been retrieved for the current reporting interval.

Cumulatively, 7 ICSRs were retrieved (4 males, 2 females, 1 individual of unknown sex, age range 14 – 76 years, when reported). The 7 cumulative ICSRs included 7 AEs coded to PTs: Pericarditis (n=4), Carditis (n=1), Myocarditis (n=1), and Myopericarditis (n=1). Of the 7 AEs reported, 7 were serious, with the events meeting the following criteria: 7 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 3 hospitalisation.

Cases with Nuvaxovid JN.1:

Three initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (3 males, age range 42 – 45 years, when reported). The 3 cumulative ICSRs included 3 AEs coded to PTs: Pericarditis (n=2) and Myopericarditis (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): 3 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 1 hospitalisation.

15.2.26.3.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 myocarditis and pericarditis using the following risk windows: 0 – 7 days, 0 – 14 days, 0 – 30 days, and 0 – 42 days (refer to Table 39 for risk windows).

For the report [redacted], a pericarditis AE with TTO of 25 days appeared due to the database's auto calculation from the 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 24 for stratification of AEs included in O/E analysis.

Table 24: Stratification of AEs Included in Unadjudicated O/E Analysis for Myocarditis and Pericarditis by vaccine

Parameters	Novavax COVID-19 Vaccines	Nuvaxovid	Nuvaxovid XBB 1.5	Nuvaxovid JN.1
Total ICSRs	99	89	7	3
Total AEs	101	91	7	3
Number of AEs with TTO reported	64	58	4	2
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	37	33	3	1
AEs with TTO falling outside risk windows (All AEs)				
Risk window 0 – 7 days	21	19	2	0
Risk window 0 – 14 days	10	9	1	0
Risk window 0 – 30 days	4	4	0	0
Risk window 0 – 42 days	3	3	0	0
Total AEs included in O/E analysis stratified by risk window (All AEs)				
Risk window 0 – 7 days	78	70	5	3
Risk window 0 – 14 days	89	80	6	3
Risk window 0 – 30 days	95	85	7	3
Risk window 0 – 42 days	96	86	7	3
Total AEs included in O/E age and gender stratified analysis (All AEs)				
Risk window 0 – 42 days	96	Not Applicable	Not Applicable	Not Applicable

Risk window 0 – 7 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=78), the unadjudicated observed rate was significantly greater than expected with an RR of

3.82 (95% CI: 3.02 – 4.77). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=70) with an RR of 5.52 (95% CI: 4.30 – 6.97) but not greater than expected for Nuvaxovid XBB.1.5 (n=5). The observed rate was non-significantly greater than expected for Nuvaxovid JN.1 (n=3).

Risk window 0 – 14 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=89), the unadjudicated observed rate was significantly greater than expected with an RR of 2.18 (95% CI: 1.75 – 2.68). When assessing by vaccine formulation, the unadjudicated observed rate was significantly greater than expected for Nuvaxovid (n=80) with an RR of 3.15 (95% CI: 2.50 – 3.92), but lower than expected for Nuvaxovid XBB.1.5 (n=6) and Nuvaxovid JN.1 (n=3).

Risk window 0 – 30 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=95), the unadjudicated observed rate was non-significantly greater than expected. When assessing by vaccine formulation, 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=7) and Nuvaxovid JN.1 (n=3).

Risk window 0 – 42 days: When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=96), the unadjudicated observed rate was lower than expected. When assessing by vaccine formulation, 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=7) and Nuvaxovid JN.1 (n=3).

Table 25: 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	3.82 (3.02 – 4.77) [1]	7.64 (6.649 – 8.92) [1]	15.29 (13.64 – 17.06) [1]
0 – 14 Days	2.18 (1.75 – 2.68) [1]	4.36 (3.74 – 5.04) [1]	8.72 (7.84– 9.66) [1]
0 – 30 Days	1.14 (0.92 – 1.39)	2.28 (1.97 – 2.62) [1]	4.56 (4.11 – 5.03) [1]
0 – 42 Days	0.85 (0.69 – 1.04)	1.70 (1.47 – 1.96) [1]	3.41 (3.07 – 3.76) [1]
Nuvaxovid			
0 – 7 Days	5.52 (4.30 – 6.97) [1]	11.03 (9.28 – 12.98) [1]	22.06 (19.55 – 24.76) [1]
0 – 14 Days	3.15 (2.50 – 3.92) [1]	6.30 (5.36 – 7.34) [1]	12.61 (11.26 – 14.04) [1]
0 – 30 Days	1.68 (1.34 – 2.08) [1]	3.36 (2.87 – 3.89) [1]	6.72 (6.02 – 7.46) [1]
0 – 42 Days	1.28 (1.02 – 1.58) [1]	2.55 (2.19 – 2.96) [1]	5.11 (4.58 – 5.67) [1]

Table 25: Unadjudicated O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

Nuvaxovid XBB.1.5			
0 – 7 Days	0.99 (0.32 – 2.31)	1.98 (0.95 – 3.52)	3.97 (2.42 – 6.00) [1]
0 – 14 Days	0.60 (0.22 – 1.30)	1.19 (0.61 – 2.02)	2.38 (1.53 – 3.48) [1]
0 – 30 Days	0.32 (0.13 – 0.67) [2]	0.65 (0.35 – 1.06)	1.30 (0.86– 1.85)
0 – 42 Days	0.23 (0.09 – 0.48) [2]	0.46 (0.25 – 0.76) [2]	0.93 (0.62 – 1.32)
Nuvaxovid JN.1			
0 – 7 Days	1.12 (0.23 – 3.28)	2.24 (0.82 – 4.62)	4.48 (2.32 – 7.59) [1]
0 – 14 Days	0.56 (0.12 – 1.64)	1.12 (0.41 – 2.31)	2.24 (1.16 – 3.80) [1]
0 – 30 Days	0.27 (0.06 – 0.78) [2]	0.54 (0.20 – 1.11)	1.07 (0.55 – 1.82)
0 – 42 Days	0.20 (0.04 – 0.58) [2]	0.40 (0.14 – 0.81) [2]	0.79 (0.41 – 1.34)

[1] Observed rates significantly greater than expected.

[2] Observed rates significantly less than expected.

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

When accounting for All-NVX-COVID-19 Vaccines cumulative myocarditis and pericarditis reports with a risk window of 0 – 42 days (n=96), stratified by age and sex, the unadjudicated observed rate as reported for the total male group (n=47) and the total female group (n=48) were non-significantly greater than expected. The unadjudicated observed rate was significantly greater than expected in the 0 – 19-year-old male group (n=4) with an RR of 7.43 (95% CI: 2.03 – 19.03) and in the 20 – 29-year-old male group (n=13) with an RR of 2.70 (95% CI: 1.44 – 4.62). Significantly greater than expected unadjudicated observed rates were observed in the 20 – 29-year-old female group (n=11) with an RR of 4.93 (95% CI: 2.46 – 8.83) and in the 40 – 49-year-old female group (n=13) with an RR of 2.04 (95% CI: 1.09 – 3.49).

Table 26: Unadjudicated O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex (Risk Window 0 – 42 Days)

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	7.43 (2.03 – 19.03) [1]	0	0 (0 – 28.83)
20 – 29	13	2.70 (1.44 – 4.62) [1]	11	4.93 (2.46 – 8.83) [1]
30 – 39	7	0.99 (0.40 – 2.05)	10	2.00 (0.96 – 3.69)
40 – 49	10	1.65 (0.79 – 3.03)	13	2.04 (1.09 – 3.49) [1]
50 – 59	6	0.94 (0.35 – 2.06)	6	0.73 (0.27 – 1.58)
60 – 69	0	0 (0 – 0.60)	5	0.69 (0.22 – 1.61)
70 – 79	1	0.21 (<0.01 – 1.15)	1	0.21 (<0.01 – 1.16)

Table 26: Unadjudicated O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex (Risk Window 0 – 42 Days)

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
80+	1	0.55 (0.02 – 3.07)	0	0 (0 – 1.85)
Missing	5	Not Applicable	2	Not Applicable
Total	47	1.25 (0.92 – 1.66)	48	1.33 (0.98 – 1.77)

[1] Observed rates significantly greater than expected.

15.2.26.3.2.2 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.

15.2.26.3.3 Conclusion

For All-NVX-COVID-19 Vaccines, the unadjudicated O/E results for cumulative myocarditis and pericarditis showed significantly greater than expected rates for the 0 – 7 and 0 – 14 day risk windows. For Nuvaxovid, the unadjudicated observed rate of cumulative myocarditis and pericarditis was significantly greater than expected for all risk windows.

The unadjudicated O/E analyses for All-NVX-COVID-19 Vaccines stratified by age and sex revealed a significantly greater than expected observed rate in the 0 – 29-year-old male group, the 20 – 29-year-old female group and the 40 – 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.

15.2.27 Narcolepsy

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for narcolepsy (refer to Appendix 12).

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:

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

Cases with Nuvaxovid JN.1:

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

15.2.27.2 Conclusion

No safety signal was identified.

15.2.28 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 12).

15.2.28.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.28.2 Conclusion

No safety signal was identified.

15.2.29 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 12).

15.2.29.1 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 were retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, 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).

Cases with Nuvaxovid JN.1:

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

15.2.29.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid XBB.1.5 (n=1). No cases were reported for Nuvaxovid and Nuvaxovid JN.1.

15.2.29.3 Conclusion

The single ICSR met TTO inclusion criteria and results of unadjudicated O/E and sensitivity analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid XBB.1.5.

No safety signal was identified.

15.2.30 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 12).

15.2.30.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.30.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). O/E and sensitivity analyses showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=1). No cases were reported for Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

15.2.30.3 Conclusion

A single ICSR met the TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.31 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 12).

15.2.31.1 Results and Discussion

Cases with Nuvaxovid:

One initial and 1 follow-up ICSR was retrieved for the current reporting interval.

Cumulatively, 6 ICSRs were retrieved (2 male, 4 females, age range 26 – 50 years). The 6 cumulative ICSRs included 6 AEs coded to PT: Postural orthostatic tachycardia syndrome (n=6). Of the 6 AEs reported, 2 were serious, with the events meeting the following criteria: 1 medically significant (based on medical judgement) and 1 hospitalisation.

Cases with Nuvaxovid XBB.1.5:

No 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.

Cases with Nuvaxovid JN.1:

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

15.2.31.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO for 3 of 7 AEs were reported as 0, 3, and 4 days, which fell within the risk window of 0 – 42 days (refer to Table 39). TTO were not reported for 3 AEs, and they were conservatively assumed to fall within the risk window of 0 – 42 days. TTO for 1 AE was reported as 68 days, which fell outside the risk window. Therefore, after excluding 1 AE from the analysis, 6 AEs met the inclusion criteria

for the observed count (n=6). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for both Nuvaxovid (n=5) and Nuvaxovid XBB.1.5 (n=1). No cases were reported for Nuvaxovid JN.1.

15.2.31.3 Conclusion

Six ICSRs met inclusion criteria for the observed count and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid XBB.1.5.

No safety signal was identified.

15.2.32 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 12).

15.2.32.1 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:

No ICSRs were 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).

Cases with Nuvaxovid JN.1:

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

15.2.32.2 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.

15.2.32.3 Conclusion

No safety signal was identified.

15.2.33 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 12).

15.2.33.1 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:

No ICSRs were 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.

Cases with Nuvaxovid JN.1:

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

15.2.33.2 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.

15.2.33.3 Conclusion

No safety signal was identified.

15.2.34 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 12).

15.2.34.1 Results and Discussion

Cases Nuvaxovid:

No 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:

No ICSRs have been 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).

Cases with Nuvaxovid JN.1:

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

15.2.34.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). The TTO were 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 for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for both Nuvaxovid (n=6) and Nuvaxovid XBB.1.5 (n=1). No cases were reported for Nuvaxovid JN.1.

15.2.34.3 Conclusion

Seven ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid XBB.1.5.

No safety signal was identified.

15.2.35 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 12).

15.2.35.1 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:

No ICSRs have been 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).

Cases with Nuvaxovid JN.1:

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

15.2.35.2 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.

15.2.35.3 Conclusion

No safety signal was identified.

15.2.36 Stillbirth

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for stillbirth (refer to Appendix 12).

15.2.36.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.36.2 Conclusion

No safety signal was identified.

15.2.37 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 12).

15.2.37.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were 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:

No ICSRs were 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.

Cases with Nuvaxovid JN.1:

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

15.2.37.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines 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 39). Therefore, 2 of 2 events met the inclusion criteria for the observed count (n=2). The O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for both Nuvaxovid (n=1) and Nuvaxovid XBB.1.5 (n=1). No cases were reported for Nuvaxovid JN.1.

15.2.37.3 Conclusion

Two ICSRs met TTO inclusion criteria and results of unadjudicated O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid XBB.1.5. No cases were reported for JN.1.

No signal was identified.

15.2.38 Thrombocytopenia

The global vaccine safety database was queried for interval and cumulative ICSRs using the pre-specified search strategy for thrombocytopenia (refer to Appendix 12).

15.2.38.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs have been 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 15.2.39).

Cases with Nuvaxovid XBB.1.5:

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

Cases with Nuvaxovid JN.1:

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

15.2.38.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 fell within the risk window of 0 – 42 days (refer to Table 39). TTO were 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-NVX-COVID-19 Vaccines, the unadjudicated O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=9). No cases were reported for Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

15.2.38.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.39 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 12).

15.2.39.1 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 15.2.38).

Cases with Nuvaxovid XBB.1.5:

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

Cases with Nuvaxovid JN.1:

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

15.2.39.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO for this single report was 6 days, which fell within the risk window of 0 – 28 days (refer to Table 39). O/E and sensitivity analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=1). No cases were identified for Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

15.2.39.3 Conclusion

The single ICSR met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines and Nuvaxovid.

No safety signal was identified.

15.2.40 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 12).

15.2.40.1 Results and Discussion

Cases with Nuvaxovid:

No ICSRs were 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 (based on medical judgement or serious by convention, 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 (based on medical judgement or serious by convention, meeting IME criteria).

Cases with Nuvaxovid JN.1:

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

15.2.40.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO for one AE was reported as 11 days. TTO for the second AE was not reported, which was conservatively included in O/E analyses. O/E analyses for All-NVX-COVID-19 Vaccines showed that the unadjudicated observed rate was lower than the expected rate. At 75% underreporting, the observed rate was non-significantly greater than expected. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for Nuvaxovid (n=1), unless assuming 75% underreporting where the observed rate was non-significantly greater than expected. The unadjudicated observed rate for Nuvaxovid XBB.1.5 (n=1) was lower than expected. No cases were identified for Nuvaxovid JN.1.

15.2.40.3 Conclusion

All ICSRs met TTO inclusion criteria and results of the O/E and 50% sensitivity analyses showed lower than expected rates for the All-NVX-COVID-19 Vaccines.

No safety signal was identified.

15.2.41 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 12).

15.2.41.1 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.

Cases with Nuvaxovid JN.1:

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

15.2.41.2 Results of Unadjudicated O/E Analysis

O/E analyses were 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.

15.2.41.3 Conclusion

No safety signal was identified.

15.2.42 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 12).

15.2.42.1 Results and Discussion

Cases with Nuvaxovid:

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

Cumulatively, 25 ICSRs were retrieved (10 males, 13 females, 2 individuals of unspecified sex, age range 26 – 85 years, when reported). The 25 cumulative ICSRs included 30 AEs coded to PTs: Pulmonary embolism (n=15), Deep vein thrombosis (n=5), Thrombophlebitis (n=4), Venous thrombosis (n=3), Superficial vein thrombosis (n=2), and Cerebral venous sinus thrombosis (n=1). Of the 30 AEs reported, 25 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 23 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 17 hospitalisation, 5 life-threatening, and 1 disability.

Cases with Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (1 male, 2 females, age range 31 - 76 years) and included 4 serious AEs coded to PTs: Pulmonary Embolism (n=2), Deep Vein Thrombosis (n=1) and Subclavian Vein Thrombosis (n=1). The 4 serious AEs met the following seriousness criteria (an event may meet more than one seriousness criterion): 4 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 hospitalisation.

Cases with Nuvaxovid JN.1:

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

15.2.42.2 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, 28 AEs were considered for O/E analysis for the risk window of 0 – 28 days (refer to Table 39). The TTO for 19 of the 28 AEs ranged from 1 – 28 days. TTO was not reported for 1 AE, which was conservatively included in O/E analyses. The TTO for the other 8 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-NVX-COVID-19 Vaccines, the unadjudicated O/E and sensitivity analyses showed that the observed rate was lower than the expected rate. When assessing by vaccine formulation, the unadjudicated observed rate was lower than expected for both Nuvaxovid (n=18) and Nuvaxovid XBB.1.5 (n=2). No cases were identified for Nuvaxovid JN.1.

15.2.42.3 Conclusion

Twenty AEs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid and Nuvaxovid XBB.1.5.

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-Dec-2024 according to the prespecified search strategies for the safety topics listed below (refer to Appendix 13 for search strategies 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 13).

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 35 ICSRs were retrieved (20 males, 14 females, 1 individual of unknown sex, age range 13 – 96 years, when reported). The 35 cumulative ICSRs included 60 fatal AEs coded to PTs (n>1) Death (n=15), Dyspnoea (n=4), Pyrexia (n=3), Adverse event following immunisation (n=2), Cerebrovascular accident (n=2), Dizziness (n=2), and Headache (n=2).

Cases with Nuvaxovid XBB.1.5:

One follow-up ICSR was 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).

Cases with Nuvaxovid JN.1:

Five initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (2 males, 2 females, 1 individual of unknown sex, age range 57 – 88 years, when reported). The 5 cumulative ICSRs included 6 fatal AEs coded to PTs: Myocardial infarction (n=3), Death (n=2), and Pulseless electrical activity (n=1).

15.3.1.1 Results of O/E Analysis

An All-NVX-COVID-19 Vaccines O/E analysis was performed in addition to formulation-specific O/E analyses.

For the All-NVX-COVID-19 Vaccines O/E analysis, TTO in 35 of 47 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 39). Three reports with fatal outcome fell outside the risk window and were excluded from the O/E. TTO were not reported for the other 9 reports, and these were conservatively included as falling within the risk window. Therefore, 44 of 47 reports met inclusion criteria for O/E (n=44) and the observed rate was lower than the expected rate. When assessing by vaccine formulation, the observed rate was lower than expected for Nuvaxovid (n=31), Nuvaxovid XBB.1.5 (n=8) and Nuvaxovid JN.1 (n=5).

15.3.1.2 Conclusion

Forty-four ICSRs met TTO inclusion criteria and results of the O/E analyses showed lower than expected rates for All-NVX-COVID-19 Vaccines, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1.

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 13).

Cases with Nuvaxovid:

No ICSRs have been 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:

No ICSRs have been 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).

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, one ICSR was retrieved (1 female, 53 years). The ICSR included 1 AE coded to PT: Blood alkaline phosphatase increased (n=1), which was non-serious.

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 13).

Cases with Nuvaxovid:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 139 ICSRs were retrieved (28 males, 110 females, 1 individual of unspecified gender, age range 18 – 86 years, when reported). The 139 cumulative ICSRs included 140 AEs coded to the PT of Diarrhoea. Of the 140 AEs reported, 24 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), 13 hospitalisation, and 2 disability.

Cases with Nuvaxovid XBB.1.5:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 9 ICSRs were retrieved (5 males, 4 females, age range 31 - 95 years, when reported). The 9 cumulative ICSRs included 9 AEs coded to PT of Diarrhoea. Of the 9 AEs reported, 1 was serious, with the event meeting the following criteria: hospitalisation.

Cases with Nuvaxovid JN.1:

Seven initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 7 ICSRs were retrieved (3 males, 3 females, 1 individual of unspecified gender, age range 34 - 77 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 13).

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, 2 ICSRs were retrieved (2 males, ages 41 years and unknown age). The 2 ICSR included 2 non-serious AEs coded to PT Herpes zoster (n=2).

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, 42 years old). The ICSR included 1 AE coded to PT: Herpes zoster (n=1), which was non-serious.

15.3.4.1 Results of Unadjudicated O/E Analysis

An All-NVX-COVID-19 Vaccines 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 rates were lower than the expected rates for all risk windows and all formulations.

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 13).

Cases with Nuvaxovid:

Two 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:

No ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 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).

Cases with Nuvaxovid JN.1:

Five initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (2 males, 3 females, age range 35 – 67 years, when reported). The 5 cumulative ICSRs included 7 AEs coded to PTs: Eye swelling (n=3), Eye discharge (n=1), Eye pruritus (n=1), Photophobia (n=1), and Ocular hyperaemia (n=1). Of the 7 AEs reported none were serious.

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 13).

Cases with Nuvaxovid:

No ICSRs have been 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.

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 females, 39 years). The ICSR included 1 AE coded to PT: Heavy menstrual bleeding (n=1), which was non-serious.

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 13).

Cases with Nuvaxovid:

Four initial and 1 follow-up ICSRs were retrieved during the current reporting interval.

Cumulatively, 419 ICSRs were retrieved (109 males, 308 females, 2 individuals of unspecified sex, age range 13 – 81 years, when reported). The 419 cumulative ICSRs included 519 AEs coded to PTs Paraesthesia (n=310), Hypoaesthesia (n=138), Burning sensation (n=39), Skin burning sensation (n=14), Hyperaesthesia (n=8), Dysaesthesia (n=8), and Hemiparaesthesia (n=2). Of the 519 AEs reported, 75 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 46 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 27 hospitalisation, 7 disability, 1 congenital anomaly/birth defect.

Cases with Nuvaxovid XBB.1.5:

Two initial ICSRs were retrieved during the current reporting interval.

Cumulatively, 21 ICSRs were retrieved (5 males, 16 females, age range 28 – 77 years, when reported). The 21 cumulative ICSRs included 27 AEs coded to PTs Paraesthesia (n=17), Hypoaesthesia (n=8), Skin burning sensation (n=1), and Dysaesthesia (n=1). Of the 27 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.

Cases with Nuvaxovid JN.1:

Thirteen initial ICSRs were retrieved during the current reporting interval.

Cumulatively, 13 ICSRs were retrieved (1 males, 12 females, age range 21 – 80 years, when reported). The 13 cumulative ICSRs included 15 AEs coded to PTs Paraesthesia (n=5), Hypoaesthesia (n=7), and Burning sensation (n=3). Of the 15 AEs reported, 2 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 1 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 13).

Cases with Nuvaxovid:

One initial and 27 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 321 ICSRs were retrieved (90 males, 218 females, 13 individuals of unspecified sex, age range 12 – 93 years, when reported), of which 147 ICSRs contained lot numbers. The 321 cumulative ICSRs included 856 AEs, with the most frequently reported PTs ($n \geq 50$): Headache (n=124), Fatigue (n=118), Pyrexia (n=84), Injection site pain (n=83), Myalgia (n=55), Malaise (n=53), and Nausea (n=50). Of the 856 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:

Three initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 12 ICSRs were retrieved (3 males, 7 females, and 2 individuals of unspecified sex, age range 35 – 80 years, when reported), of which 7 ICSRs contained a lot number. The 12 cumulative ICSRs included 24 AEs coded to Fatigue (n=4), Vaccination site pain (n=4), Headache (n=2), Pyrexia (n=2), Asthenia (n=1), Injection site discolouration (n=1), Injection site erythema (n=1), Injection site mass (n=1), Injection site pruritus (n=1), Malaise (n=1), Muscular weakness (n=1), Myalgia (n=1), Vaccination site erythema (n=1), Vaccination site induration (n=1), Vaccination site mass (n=1), and Vaccination site swelling (n=1). Of 24 AEs, 1 was serious due to medically significant seriousness criteria (based on medical judgement).

No trends related to reactogenicity based on impurity levels specifically after a second dose and/or a booster were identified.

Cases with Nuvaxovid JN.1:

Nine initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 9 ICSRs were retrieved (2 males, 6 females, and 1 individual of unspecified sex, age range 25 – 75 years, when reported), of which 5 ICSRs contained a lot number. The 9 cumulative ICSRs included 17 non-serious AEs coded to PTs: Vaccination site pain (n=4), Malaise (n=2), Nausea (n=2), Feeling abnormal (n=1), Headache (n=1), Injection site erythema (n=1), Injection site reaction (n=1), Injection site swelling (n=1), Injection site warmth (n=1), Pyrexia (n=1), Vaccination site pruritus (n=1), and Vaccination site urticaria (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 13).

15.3.9.1 Review of Safety Concerns in Elderly

Cases with Nuvaxovid:

Five initial and 5 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 734 ICSRs were retrieved (256 males, 471 females, 7 individuals of unknown sex, age range 65 – 96 years, when reported). These 734 ICSRs included 2150 AEs. The 5 most frequently reported AEs were coded to PTs Myalgia (n=137), Headache (n=117), Dizziness (n=87), Hypersensitivity (n=85), and Injection site pain (n=62). Of the 2,150 AEs, 444 AEs were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 267 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 209 hospitalisation, 64 disability, 7 life-threatening and 43 fatal AEs.

Cases with Nuvaxovid XBB.1.5:

Fifteen initial and 3 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 112 ICSRs were retrieved (44 males, 66 females, 2 individual of unknown sex, age range 65 – 95 years, when reported). The 112 cumulative ICSRs included 413 AEs coded to PTs (n≥10): Headache (n=16), Pain in extremity (n=15), Pyrexia (n=15), Fatigue (n=13),

Dizziness (n=11), Expired product administered (n=11), and Product storage error (n=10). Of the 413 AEs reported, 84 were serious, with the events meeting the following criteria (an event may meet more than one seriousness criterion): 53 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.

Cases with Nuvaxovid JN.1:

One hundred and twenty-one initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 121 ICSRs were retrieved (49 males, 65 females, 7 individual of unknown sex, age range 65 – 99 years, when reported). The 121 cumulative ICSRs included 297 AEs coded to PTs (n≥10): Pyrexia (n=15), Headache (n=14) and Pain (n=10). Of the 121 AEs reported, 67 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), 35 hospitalisation, 11 disability, 6 life-threatening and 3 fatal AEs.

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 who were exposed to vaccine as a foetus 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, 4 ICSRs were retrieved (3 males, age 8, 9 years and infant, and 1 female neonate). The 4 cumulative ICSRs included 7 non-serious AEs.

Two of the 4 ICSRs 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).

Two of the 4 ICSRs were reported in the neonatal and infant age group who were exposed to vaccine as a foetus. The 2 ICSRs included 5 AEs coded to PTs: Influenza (n=1), Nasopharyngitis (n=1), Premature baby (n=1) and Foetal exposure during pregnancy (n=2).

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (1 male, 1 female, age 5 and 8 years). The 2 cumulative ICSRs included 7 AEs coded to PTs: Wrong patient (n=1), Pain in extremity (n=1), Product administered to patient of inappropriate age (n=1), Decreased appetite (n=1). Abdominal pain (n=1), Headache (n=1), and Vomiting (n=1). All 7 AEs were non-serious.

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 Food and Drug Administration (FDA) (27-Sep-2023) and European Medicines Agency (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 13).

Cases with Nuvaxovid:

No ICSRs have been 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:

One initial ICSR was retrieved during the current reporting interval.

Cumulatively, 10 ICSRs were retrieved (2 males, 6 females, 2 individual of unspecified sex, age range 30 – 71 years, when reported). The 10 cumulative ICSRs included 10 non-serious AEs coded to PT Tinnitus.

Cases with Nuvaxovid JN.1:

Three initial ICSRs were retrieved during the current reporting interval.

Cumulatively, 3 ICSRs were retrieved (1 male, 2 females, age range 38 - 66 years). The 3 cumulative ICSRs included 3 AEs coded to PT Tinnitus. Of 3 reported AEs, 1 was serious with seriousness criteria reported as disability.

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 13).

Cases with Nuvaxovid:

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

Cumulatively, 60 ICSRs were retrieved (7 males, 48 females, 5 of unspecified sex, age range 19 – 75 years, when reported). The 60 cumulative ICSRs included 60 AEs coded to PTs: Anxiety (n=45), Nervousness (n=6), Agitation (n=4), Stress (n=3), Immunisation stress-related response (n=1), and Tension (n=1). Of the 60 AEs reported, 8 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 disability.

Cases with Nuvaxovid XBB.1.5:

One follow-up ICSR has 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.

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (2 females, age 26 years, when reported). The 2 cumulative ICSRs included 4 AEs coded to PTs: Anxiety (n=3), and Nervousness (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 13).

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:

Two follow-up ICSRs were retrieved for the current reporting 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:

Four initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 10 ICSRs were retrieved (2 male, 4 females, and 4 individuals of unspecified sex, age range 46-77 years, when reported). The 10 cumulative ICSRs included 10 AEs, coded to PTs: Vaccination failure (n=8), and Drug ineffective (n=2). Of 10 reported AEs, 9 were serious due to medically significant criteria (based on medical judgement).

Cases with Nuvaxovid JN.1:

Two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 2 ICSRs were retrieved (1 male of unspecified age and 1 individual of unspecified sex and age). The 2 cumulative ICSRs included 2 AEs, coded to PTs: Drug ineffective (n=1) and Vaccination failure (n=1). Of 2 reported AEs, 1 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 27, obtained from the EU Risk Management Plan (RMP) v5.1, dated 14-Jun-2024. During the reporting period, the EU RMP was updated to v6.1, dated 31-Oct-2024 to support the prefilled syringe presentation of the JN.1 variant-adapted vaccine. There were no changes to the list of safety concerns during the above-mentioned revision.

Table 27: 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
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

No new signals were validated during the current reporting interval.

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 15.2.26 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:

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

Cumulatively, 138 ICSRs were retrieved (60 males, 78 females, age range 18 – 83 years, when reported). The 138 cumulative ICSRs included 173 AEs, with the most frequently reported PTs (n≥5): Pericarditis (n=57), Myocarditis (n=24), Electrocardiogram abnormal (n=13), Extrasystoles (n=12), Myopericarditis (n=7), Troponin increased (n=7), Ventricular extrasystoles (n=7), Pericardial effusion (n=6), and Echocardiogram abnormal (n=5). Of the 173 AEs reported, 138 were serious, with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 130 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 49 hospitalisation, 5 life-threatening, and 3 deaths. Of these 138 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 28 and Table 29, respectively.

Cases with Nuvaxovid XBB1.5:

Three initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 18 ICSRs were retrieved (10 males, 7 females, 1 of unknown sex, age range 14 – 91 years, when reported). The 18 cumulative ICSRs included 21 AEs, with the most frequently reported PTs (n≥3): Extrasystoles (n=5), and Pericarditis (n=4). Of the 21 AEs reported, 13 were serious, with the events meeting the following criteria: 12 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 5 hospitalization, 1 life-threatening, and 2 death. Of these 18 ICSRs, 1 met Level 1 – 3 Brighton Collaboration case definitions for myocarditis and/or pericarditis.

Demographics and case characteristics of the case that met a case definition are summarised in Table 28 and Table 29, respectively.

Cases with Nuvaxovid JN.1:

Five initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 5 ICSRs were retrieved (4 males, 1 female, age range 42 – 53 years, when reported). The 5 cumulative ICSRs included 7 AEs coded to PTs: Pericarditis (n=2), Troponin increased (n=2), Ejection fraction decreased (n=1), Electrocardiogram abnormal (n=1), and Myopericarditis (n=1). Of the 7 AEs reported, 6 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 4 hospitalisation. Of these 5 ICSRs, 3 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 28 and Table 29, respectively.

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 or Nuvaxovid JN.1.

Table 28: Demographics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Sex/Age (years)	Nuvaxovid (n=52)	Nuvaxovid XBB.1.5 (n=1)	Nuvaxovid JN.1 (n=3)
	Number of Reports	Number of Reports	Number of Reports
Male	**22**	**0**	**2**
18 – 29	6	0	0
30 – 39	7	0	0
40 – 49	6	0	1
50 – 59	2	0	1
UNK	1	0	0
Female	**30**	**1**	**1**
18 – 29	4	0	0
30 – 39	8	0	0
40 – 49	5	0	0
50 – 59	8	0	1
60+	5	1	0

Table 29: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)	Nuvaxovid XBB.1.5 (n=1)	Nuvaxovid JN.1 (n=3)
		Number of Reports	Number of Reports	Number of Reports
Total		52	1	3
Myocarditis [1]		32	0	3
Pericarditis [1]		28	1	1
Country of Incidence	Australia	30	0	0
	Germany	6	0	0
	Korea, Republic of	5	0	0
	Italy	3	0	0
	France	3	0	0
	Austria	2	0	0
	Finland	1	0	0
	Greece	1	0	0
	United States	1	1	3
Seriousness Criteria [2]	Medically Significant	48	1	1
	Hospitalisation	19	0	4
	Life-threatening	1	0	0

Table 29: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)	Nuvaxovid XBB.1.5 (n=1)	Nuvaxovid JN.1 (n=3)
		Number of Reports	Number of Reports	Number of Reports
Co-reported PTs (n≥5)	Chest pain	27	1	2
	Pericarditis	18	0	0
	Dyspnoea	15	1	1
	Palpitations	10	0	0
	Myocarditis	10	0	0
	Headache	10	0	0
	Dizziness	9	0	0
	Fatigue	8	0	0
	Electrocardiogram abnormal	8	0	1
	Chest discomfort	7	1	1
	Myalgia	6	0	0
	Tachycardia	5	0	0
	Paraesthesia	5	0	0
	Arthralgia	5	0	0
	Nausea	5	0	1
Recurrent Myocarditis/Pericarditis [3]		7	0	0
BC Level [4,8]	Level 1	5	0	1
	Level 2	34	1	1
	Level 3	9	0	1
	Level 1 – 3 (exact level unknown) [6]	4	0	0
Time to Onset (Days) [5]	0 – 7	26	1	1
	8 – 14	9	0	0
	> 15	7	0	2

Table 29: Report Characteristics of ICSRs Meeting Brighton Collaboration Levels 1 – 3 for Myocarditis and/or Pericarditis

Parameters		Nuvaxovid (n=52)	Nuvaxovid XBB.1.5 (n=1)	Nuvaxovid JN.1 (n=3)
		Number of Reports	Number of Reports	Number of Reports
	UNK	10	0	0
Outcome [7]	Unknown	28	0	1
	Not Recovered/Not Resolved/Ongoing	24	2	4
	Recovering/Resolving	9	0	0
	Recovered/Resolved	7	0	0
	Recovered/Resolved with Sequelae	2	0	0

[1] Some cases are included in both the myocarditis and pericarditis categories.

[2] Reflects event level seriousness of PTs that were retrieved by the search strategy. Some ICSRs have more than one event retrieved by the search strategy.

[3] Classification of recurrent myocarditis/pericarditis refer to reports where the previous myocarditis/pericarditis or reported chest pain was experienced after vaccination with a non-company product, viral infection, or unknown cause.

[4] If a case met a different level of certainty for myocarditis and pericarditis, then the highest level was chosen for representation in this section.

[5] 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.

[6] Adjudication is based on assessment by KDCA against modified Brighton collaboration.

[7] 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 15.2.41.

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 15.2.4. 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 13).

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 13).

16.3.5.1.1.1 Results and Discussion

Cases with Nuvaxovid:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 16 ICSRs were retrieved (14 females, age range 19 – 57 years) with 44 AEs. The 16 ICSRs had 20 pregnancy associated PTs: Abortion spontaneous (n=4), Maternal exposure during pregnancy (n=9), Exposure during pregnancy (n=2), Pre-eclampsia (n=2), Gestational hypertension, Placental infarction, Premature delivery (n=1 each). Of the total 44 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 1 hospitalization.

Cases with Nuvaxovid XBB.1.5:

No 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).

Cases with Nuvaxovid JN.1:

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

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-Dec-2024 for the patient age group of foetus and neonate and retrieved ICSRs are manually reviewed to confirm exposure during pregnancy.

16.3.5.1.2.1 Results and Discussion

Cases with Nuvaxovid:

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

Cumulatively, 4 ICSRs were retrieved (1 male, 2 females, 1 individual of unspecified gender; age group:1 foetus and 3 neonates), all. were exposed to Nuvaxovid 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 Nuvaxovid XBB.1.5:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 4 ICSRs were retrieved (2 male foetus, 1 foetus of unspecified gender and 1 female neonate). The neonate was exposed to Nuvaxovid XBB 1.5 via transplacental route. The 4 cumulative ICSRs included 10 AEs coded to PTs: Foetal exposure during pregnancy (n=4), Large for dates baby (n=2), Premature baby (n=1), Ventricular septal defect (n=1), Congenital aortic valve stenosis (n=1), and Foetal heart rate deceleration abnormality (n=1). Of the 10 AEs reported, 3 AEs were serious with the events meeting the following criteria: 3 medically significant (based on medical judgement or serious by convention, meeting IME criteria) and 2 congenital anomaly.

Cases with Nuvaxovid JN.1:

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

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 13).

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.

Cases with Nuvaxovid JN.1:

One initial ICSR was retrieved for the current reporting interval.

Cumulatively, 1 ICSR was retrieved (1 female, age unknown). The ICSR included 1 non-serious AE coded to PT: Maternal exposure during breast feeding (n=1). This non-serious report of use during breastfeeding does not raise any safety concerns.

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 13).

16.3.5.2.1 Results and Discussion

Cases with Nuvaxovid:

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

Cumulatively, 31 ICSRs were retrieved (5 males, 21 females, 5 of unspecified sex, age range 35 – 93 years). The 31 cumulative ICSRs included 108 AEs. The most frequently reported AEs (n>1) included: Off label use (n=8), COVID-19 immunisation (n=8), 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 108 AEs reported, 33 were serious with the events meeting the following criteria (an event may meet more than 1 seriousness criterion): 29 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:

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

Cumulatively, 9 ICSRs were retrieved (1 male, 4 females, 4 of unspecified sex, age range 63 – 69 years, when reported). The 9 cumulative ICSRs included 28 AEs. The most frequently

reported AEs (n>1) included: COVID-19 (n=4), Asthenia (n=2), Pain in extremity (n=2), and Sinus congestion (n=2). Of the 28 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.

Cases with Nuvaxovid JN.1:

Seven initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 7 ICSRs were retrieved (2 males, 3 females, 2 of unspecified sex, age range 43 – 72 years, when reported). The 7 cumulative ICSRs included 20 AEs coded to PTs: Headache (n=4), Fatigue (n=2), Nausea (n=2), and Pain (n=2). Of the 20 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).

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 13).

16.3.5.3.1 Results and Discussion

Cases with Nuvaxovid:

Nine initial and 17 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 656 ICSRs were retrieved (170 males, 456 females, 30 individuals of unspecified sex, age range 13 – 96 years, when reported). The 656 cumulative ICSRs included 2911 AEs. The most frequently reported PTs (n>50) were Headache (n=124), Fatigue (n=116), Myalgia (n=71), Pyrexia (n=68), Dizziness (n=59), Chest pain (n=56), Injection site pain (n=54), Pain in extremity (n=53), and Nausea (n=53). Of the 2911 AEs reported, 780 were serious (including 21 fatal AEs).

Cases with Nuvaxovid XBB.1.5:

Thirteen initial and 4 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 144 ICSRs were retrieved (40 males, 84 females, 20 individuals of unspecified sex, age range 14 – 94 years, when reported). The 144 cumulative ICSRs included 590 AEs. The most frequently reported PTs (n≥10) were Pain in extremity (n=25), Fatigue (n=20), Pyrexia (n=17), Headache (n=16), COVID-19 (n=15), Maternal exposure during pregnancy (n=13), Pain (n=12), Unevaluable event (n=11), Nausea (n=10), and Dizziness (n=10). Of the 590 AEs reported, 85 were serious (including 20 fatal AEs).

Cases with Nuvaxovid JN.1:

Eighty-nine initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 89 ICSRs were retrieved (26 males, 61 females, 2 individual of unspecified sex, age range 14 - 94 years, when reported). The 89 cumulative ICSRs included 388 AEs coded to PTs (n≥10): Nausea (n=14), Pain in extremity (n=12), Pyrexia (n=11), Fatigue (n=11), Headache (n=11), Dizziness (n=10), and Pain (n=10). Of the 388 AEs reported, 74 were serious (including 4 fatal AEs).

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 13).

16.3.5.4.1 Results and Discussion

Cases with Nuvaxovid:

One initial and 4 follow-up ICSRs were retrieved for the current reporting interval.

Cumulatively, 214 ICSRs were retrieved (35 males, 174 females and 5 individuals of unknown sex, age range 21 – 94 years, when reported). The 214 cumulative ICSRs included 1011 AEs. The most frequently reported AEs (n≥20) were Headache (n=45), Fatigue (n=37), Pyrexia (n=29), Myalgia (n=27), Dizziness (n=21), Nausea (n=21), Pain in extremity (n=21), and Chills (n=20). Of the 1011 AEs reported, 275 were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 215 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:

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

Cumulatively, 56 ICSRs were retrieved (15 males, 33 females and 8 individuals of unknown sex, age range 28 – 92 years, when reported). The 56 cumulative ICSRs included 244 AEs. The most frequently reported AEs (n≥5) were Pain in extremity (n=10), COVID-19 (n=8), Fatigue (n=8), Pyrexia (n=7), Headache (n=7), Dizziness (n=6), Nausea (n=6), Malaise (n=6), and Unevaluable event (n=5). Of the 244 AEs reported, 34 were serious with the events meeting the following criteria (an event may meet more than one seriousness criterion): 15 medically significant (based on medical judgement or serious by convention, meeting IME criteria), 9 hospitalisation, 1 life-threatening, 7 disability, and 13 death.

Cases with Nuvaxovid JN.1:

Forty-two initial ICSRs were retrieved for the current reporting interval.

Cumulatively, 42 ICSRs were retrieved (10 males, 32 females, age range 15 – 79 years, when reported). The 42 cumulative ICSRs included 180 AEs coded to PTs (n≥5): Nausea (n=6), Pyrexia (n=5), Headache (n=5). Of the 180 AEs reported, 24 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 [Important medical event] criteria), 13 hospitalisation, and 3 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 13).

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.

Cases with Nuvaxovid JN.1:

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 8 Table 38.

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, v6.1, dated 31-Oct-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 or Nuvaxovid JN.1. 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 three COVID-19 vaccines currently authorized in the EU – Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1– which in turn supports the benefit-risk characterisation in Section 18.

17.1 Important Baseline Efficacy and Effectiveness Information

This section provides baseline benefit information for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 at the start of the reporting interval of this PBRER (20-Jun-2024).

The baseline benefit information at the start of the PBRER reporting interval on 20-Jun-2024 is the efficacy and immunogenicity data in v10.0 of the Novavax COVID-19 Vaccine (recombinant, adjuvanted) Global CCDS dated 30-May-2024, at which time, both the Adolescent Primary Series (Main) and Adolescent Booster Parts of Study 2019nCoV-301 were ongoing. However, as summarized in Section 7.1.1 of this report, both of these Parts of Study 2019nCoV-301 were completed on 24-Sep-2024 during the current reporting interval. Therefore, both the trial status and benefit information for adolescents in this section differ from the trial status and benefit information for adolescents in Section 7.1.1 of this report.

Baseline clinical efficacy and immunogenicity of Nuvaxovid were evaluated in two pivotal, placebo-controlled, Phase 3 clinical trials: Study 2019nCoV-301 conducted in North America and Study 2019nCoV-302 conducted in the UK.

Baseline effectiveness of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 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 was supported by a study of a booster dose of an investigational vaccine targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 and BA.5 variants of SARS-CoV-2 in individuals 18 to 64 years of age.

17.1.1 Adolescents 12 to <18 years of age

17.1.1.1 Primary Series (Original, Wuhan strain)

Study 2019nCoV-301

Study 2019nCoV-301 is an ongoing Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study with an adult main study conducted in participants 18 years of age and older in US and Mexico and a pediatric expansion occurring in participants 12 through 17 years of age in the US.

17.1.1.1.1 Efficacy in Adolescents 12 to <18 years of age

The primary endpoint of effectiveness defined by non-inferior immunogenicity of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adolescent participants 12 through 17 years of age occurred in the United States in the ongoing pediatric expansion portion of the Phase 3 multicenter, randomized, observer-blinded, placebo-controlled 2019nCoV-301 study.

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 first episode of PCR-confirmed mild, moderate, or severe COVID-19 with at least one or more of the predefined 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 United States and accounted for all cases where sequence data are 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 (NP)/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], point estimate of the ratio of GMTs $\geq$ 0.82; and the lower bound of the two-sided 95% CI for difference of seroconversion rates (SCRs) (SCR 12 through 17 years minus SCR 18 through 25 years) > -10%) 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 a Phase 3, multinational, multicentre, randomized, observer-blinded, placebo-controlled Paediatric Expansion study involving 220 adolescents 12 through 17 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 through 17 years of age were seronegative to SARS-CoV-2 at baseline.

The study assessed the immune response (neutralizing antibody against SARS-CoV-2 wild-type virus, serum immunoglobulin G [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 17 years of age.

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 through 17 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 SCRs 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

Study 2019nCoV-301 - Original, Wuhan strain

Upon enrolment 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 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 (BMI) ≥ 30 kg/m2, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrolment that occurred during the time period when strains classified as Variants of Concern or Variants of Interest were predominantly circulating in the two 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

Study 2019nCoV-302 was a Phase 3, multicentre, randomized, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the United Kingdom. Upon enrolment, participants were stratified by age (18 to 64 years; 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 enrolment that occurred during the time period when the B.1.17 (Alpha) variant was circulating in the UK. 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

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.

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 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.

Study 2019nCoV-501 - Original, Wuhan strain

In Study 2019nCoV-501, a Phase 2a/b randomized, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy Human Immunodeficiency Virus (HIV) -negative adult participants 18 to 84 years of age and medically stable people living with HIV 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 Elisa Unit [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.

Study 2019nCoV-301 Original, Wuhan Strain

In the open-label booster phase of 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 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.

Prespecified 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 MN_{50} 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 enrolment 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.

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 Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adults in Australia.

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 [MN_{50}], 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 seroresponse rates. Seroresponse rate 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 seroresponse rates (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 seroresponse rates (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 seroresponse rates (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 seroresponse rates. Seroresponse rate 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% CI: 2.10, 2.94).

The difference in seroresponse rate (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% CI: 25.4%, 40.7%).

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.

In the placebo-controlled 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 Phase 3 Study 2019nCoV-302 conducted in the UK, 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

On 08-Oct-2024, the European Commission granted Marketing Authorization for Nuvaxovid JN.1 dispersion for injection COVID-19 Vaccine (recombinant, adjuvanted), for use in individuals aged 12 and older for the prevention of COVID-19 in the EU.

The effectiveness information below supporting strain change from Nuvaxovid XBB.1.5 to Nuvaxovid JN.1 was based on information summarized in the 13-Jun-2024 US FDA Decision Memo on the Emergency Use Authorization (EUA) of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula). [FDA 2024]

The clinical effectiveness data accrued with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), and monovalent vaccine (Omicron BA.1), and the clinical safety data accrued with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent), monovalent vaccine (Omicron BA.5), monovalent vaccine (Omicron BA.1), bivalent vaccine (Original and Omicron BA.1), and bivalent vaccine (Original and Omicron BA.5), are relevant to Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), because these vaccines are manufactured using a similar process. For details of previously reviewed data that support the clinical effectiveness and safety of Novavax COVID-19 Vaccine (2024-2025 Formula) for individuals 12 years of age and older, refer to [FDA 2023].

The safety and effectiveness of additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) for individuals 12 years of age and older with certain kinds of immunocompromise is based on the same evidence for use of additional doses of Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) for such individuals. [FDA 2023]

Previously reviewed data supported the clinical effectiveness and safety of Novavax COVID-19 Vaccine (2024-2025 Formula) for individuals 12 years of age and older. [FDA 2023] The effectiveness and safety of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) is based on the totality of evidence from clinical trials, including efficacy and effectiveness data

with the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) and immunogenicity data of the monovalent vaccine (Omicron BA.1) and monovalent vaccine (Omicron BA.5).

It is reasonable to expect from extrapolation of immunogenicity in individuals 12 through 17 years of age and from inference of efficacy and immunogenicity in individuals 18 years of age and older that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) may be effective in individuals 12 years of age and older. In addition, the nonclinical data reviewed indicate that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula), when used in vaccine-naïve or -experienced laboratory animals, elicited higher neutralizing antibodies compared with the Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) against JN.1-descendant variants.

Nonclinical studies were completed in mice to evaluate immunogenicity of Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) given as a two-dose primary series or as a booster. The results demonstrated that Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula) elicited strong neutralizing antibody responses against variant JN.1 and other JN.1-lineage descendant variants, including but not limited to JN.1.7, KP.2, LA.2, and KP.3 after primary and booster vaccinations compared with Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula). These data are therefore considered supportive for the formula change to Omicron JN.1-lineage variant JN.1 for the Novavax COVID-19 Vaccine, Adjuvanted (2024-2025 Formula).

17.2.1 Newly identified information on efficacy from Clinical Trials

New information on efficacy and effectiveness of the prototype vaccine primary series and of a booster dose of NVX-CoV2373 in adolescents is presented in detail in Section [7.1.1] of this report.

17.2.2 Newly identified information on efficacy and effectiveness from the literature

This sub-section provides new information that became available in the literature (6 publications) during the reporting interval of this PBRER, either on the efficacy/effectiveness (n=5) or efficacy/effectiveness and immunogenicity of Nuvaxovid vaccines (n=1).

"SARS-CoV-2-Specific Immune Cytokine Profiles to mRNA, Viral Vector and Protein-Based Vaccines in Patients with Multiple Sclerosis: Beyond Interferon Gamma" reported results of a longitudinal study to elucidate the characteristics of the involved antigen-specific T cells via the measurement of broad cytokine profiles in patients with multiple sclerosis on various disease modifying therapies. For mRNA vaccination non-responders, NVX-CoV2373 was administered, and immune responses were evaluated. The findings indicated that immune responses to SARS-CoV-2 vaccines in patients with multiple sclerosis are skewed towards a

Th1 phenotype, characterized by IL-2 and IFN-γ. Additionally, a Th2 response characterized by IL-5, and to a lesser extent IL-4, IL-10, and IL-13, is observed. Patients with multiple sclerosis non-responsive to two or three doses of mRNA or viral vector vaccines showed beneficial immune responses after receiving protein-based vaccines. [Al Rahbani 2024]

"*Relative effectiveness of homologous NVX-CoV2373 and BNT162b2 COVID-19 vaccinations in South Korea*" reported results from a retrospective cohort-study of ≥12-year-olds in South Korea after vaccination with either NVX-CoV2373 or BNT162b2 (Pfizer–BioNTech). The authors used the K-COV-N database, which links COVID-19 vaccine registry data with health insurance claims data. This real-world study on the effectiveness of NVX-CoV2373 in the general population in South Korea compared NVX-CoV2373 to BNT162b2 (Pfizer–BioNTech) in preventing SARS-CoV-2 infection and severe COVID-19 during the Omicron variant dominance in South Korea. Among homologous primary-series NVX-CoV2373 versus homologous primary-series BNT162b2 recipients at Day 180 post-vaccination, adjusted hazard ratios (aHRs) were 0.90 (95% CI: 0.87–0.93) for all laboratory-confirmed and 0.65 (95% CI: 0.48–0.88) for severe infections. Among homologous first-booster recipients, aHRs were 1.15 (95% CI: 1.01 – 1.30) for all laboratory-confirmed and 0.39 (95% CI: 0.20 – 0.75) for severe infections. At 180-days post-immunization, the authors demonstrated that the homologous NVX-CoV2373 primary-series and first booster offered comparable protection against SARS-CoV-2 infection versus BNT162b2. [Gwak]

"Association Between SARS-CoV-2 Viral Load and COVID-19 Vaccination in 4 Phase 3 Trials" reported results from the authors' analysis of the association between COVID-19 vaccine types and viral load reduction in adult participants at the time of COVID-19 diagnosis in 4 published randomized controlled phase 3 clinical trials conducted from July 2020 to July 2021. Within each trial, the distribution of viral load was lower in the vaccine group versus the placebo group. The vaccine and viral load reduction association was largest for NVX-CoV2373, with an estimated 2.78 log10 copies/mL reduction (95% CI, 1.38 – 4.18). However, the authors stated that the estimated reduction was the least precise for the Novavax trial which contributed the fewest number of COVID-19 cases. [Janes 2024]

"Relative Effectiveness of the NVX-CoV2373 Vaccine Compared With the BNT162b2 Vaccine in Adolescents" reported results from the authors' retrospective matched cohort study on the efficacy of 2 doses of NVX-CoV2373 compared to BNT162b2 vaccines in preventing SARS-CoV-2 infection in adolescents. The authors analyzed 13-week risk differences and ratios between these 2 vaccines. The study included 465 adolescents who received NVX-CoV2373 and 465 adolescents who received BNT162b2. Throughout the follow-up period, 4.1% of NVX-CoV2373 recipients and 2.8% of BNT162b2 recipients contracted the severe acute respiratory syndrome coronavirus 2 infection. The incidence risk ratio for NVX-CoV2373 compared with that for BNT162b2 was calculated at 1.46 (95% CI 0.68 – 3.22; P = 0.296). The authors stated that while their findings suggest noninferiority between the 2 vaccines, further research is needed to comprehensively assess their effectiveness in real-world settings. [Lee 2024]

"SARS-CoV-2 spike-specific nasal-resident CD49a+CD8+T cells exert immediate effector functions with enhanced IFN-γ production" Virus-specific nasal resident T cells are important for protection against subsequent infection with a similar virus. This paper reported results of the authors' study of the phenotypes and functions of SARS-CoV-2-specific T cells in the nasal mucosa of vaccinated individuals with breakthrough infection or without infection. Nasal tissues were obtained from 111 participants during sinus surgery. All patients had been immunized with BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), Ad26COV2.S (Janssen), or NVX-CoV2373 (Novavax) prior to sinus surgery and had no history of SARS-CoV-2 natural infection before vaccination. MHC-I multimer staining is performed to analyze the ex vivo phenotype and function of SARS-CoV-2 S-specific CD8+ T cells. The authors detected multimer+ CD8+ (Cluster of Differentiation 8 plus) T cells with tissue-resident phenotypes in nasal tissue samples from both vaccinees with and without breakthrough infection. The multimer+ CD8+ T cells remained in nasal tissues over one year after the last exposure to Spike (S) antigen, although the frequency decreases. Upon direct *ex vivo* stimulation with epitope peptides, nasal multimer+CD8+ T cells (particularly the CD49a+ subset) exhibited immediate effector functions, including IFN-γ production. These findings indicated that among individuals previously exposed to S antigen either by vaccination or breakthrough infection, S-specific nasal-resident CD49a+ CD8+ memory T cells can rapidly respond to SARS-CoV-2 during infection or re-infection. [Rha 2024]

"Immunogenicity and efficacy of XBB.1.5 rS vaccine against the EG.5.1 variant of SARS-CoV-2 in Syrian hamsters" presented results from the authors' study of the immunogenicity and efficacy of the XBB.1.5-adapted vaccine, the original Prototype Wuhan-1, and the bivalent Prototype + BA.5 vaccine against a challenge with the EG.5.1 Omicron variant of SARS-CoV-2 hamsters. EG.5.1 is a subvariant of the SARS-CoV-2 Omicron XBB variant. Immunization induced high levels of S-specific IgG and IgA antibody-secreting cells and antigen-specific $CD4^+$ T cells. The XBB.1.5-adapted vaccine and the bivalent vaccine, but not the Prototype, induced high levels of neutralizing antibodies against the XBB.1.5, EG.5.1, and JN.1 variants of SARS-CoV-2. Upon challenge with the Omicron EG.5.1 variant, the XBB.1.5 and XBB.1.16 vaccines reduced the virus load in the lungs, nasal turbinates, trachea, and nasal washes. The bivalent vaccine (Prototype rS + BA.5 rS) continued to offer protection in the trachea and lungs, but protection was reduced in the upper airways. By contrast, the monovalent Prototype vaccine no longer offered good protection, and breakthrough infections were observed in all animals and tissues. Thus, based on these study results, the protein-based XBB.1.5 vaccine is immunogenic and increased the breadth of protection against the Omicron EG.5.1 variant in the Syrian hamster model. [Soudani 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.

As of 15-Dec-2024, there were more than 777 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].

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), 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.

18.1.1 Benefit-Risk Analysis Evaluation

It has been 5 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 re-vaccination.

19 CONCLUSION

During the reporting interval, no new signals were validated, and no signals were generated through O/E monitoring of AESIs.

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 Nuvaxovid XBB.1.5 in Taiwan while Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) was withdrawn in US. Concurrently, NVX received either emergency use authorisation or marketing authorisation for Nuvaxovid JN.1 in Canada, EU, Japan, Singapore, South Korea, UK and US.

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, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 and support the conclusion that the overall benefit-risk balance for Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 continues to remain positive.

20 APPENDICES