NUVAXOVID: Periodic safety update report assessment

20th December 2022 to 19th June 2023

This document consists of:

1. The PRAC assessment report of the NUVAXOVID periodic safety update report (PSUR) covering the period 20th December 2022 to 19th June 2023, and;

2. The NUVAXOVID PSUR itself.

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

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

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

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

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

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

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

EMA/PRAC/585416/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010972/202306

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

Period covered by the PSUR: 20/12/2022 To: 19/06/2023

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

Status of this report and steps taken for the assessment[1]

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	14 September 2023	14 September 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 November 2023	10 November 2023
☐	MS/PRAC members and MAH comments	13 December 2023	13 December 2023
☐	PRAC Rapporteur's updated assessment report following comments	28 December 2023	19 December 2023
☐	Oral explanation	n/a	n/a
☐	PRAC recommendation	11 January 2024	11 January 2024

Procedure resources	
PRAC Rapporteur	Name: Gabriele Maurer Email: [redacted]
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Assessor – PRAC Rapporteur	Name: Tel: Email:
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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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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).

2. Assessment conclusions and actions

This assessment report relates to the 3rd periodic safety update report (PSUR) for COVID-19 vaccine (recombinant, adjuvanted), dispersion for injection (Nuvaxovid, NVX-CoV2373), with the active substance SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda*. The international birth date (IBD), as well as the European Union (EU) reference date (EURD), of Nuvaxovid is 20 December 2021, when the vaccine was granted conditional marketing authorisation by the European Medicines Agency (EMA). This PSUR covers the interval between 20 December 2022 and 19 June 2023, with the data lock point (DLP) 19 June 2023.

Nuvaxovid is a recombinant, adjuvanted protein vaccine indicated for the active immunisation to prevent Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). It contains a purified full-length SARS-CoV-2 recombinant (r) Spike (S) protein that is stabilised in its prefusion conformation and the saponin-based Matrix-M™ adjuvant. The vaccine is authorised as a two-dose primary series and as a booster in individuals 12 years and older, in India as Covovax for individuals 7 years and older. During the reporting interval, Nuvaxovid received additional authorisations for the heterologous booster indication.

The MAH reports the cumulative number of subjects exposed to the vaccine in clinical studies as 47,395. Additional 3,836 individuals received blinded treatment. The number of doses administered post-marketing is given as 329,244 in the reporting interval and 2,914,143 cumulatively. Globally, 9,790,300 and 112,787,170 doses were distributed, respectively.

During the reporting interval, the company core data sheet (CCDS) was updated to version 7.0 (effective date 02 February 2023) to include tinnitus in section 4.8 and to update safety and efficacy information in sections 4.8 and 5.1 for adolescent booster dosing. The EU risk management plan (RMP) was updated during the reporting interval to version 3.1, dated 06 February 2023, with no change in the summary of safety concerns. Myocarditis and/or pericarditis is an important identified risk, and vaccine associated enhanced disease including vaccine associated enhanced respiratory disease is an important potential risk. Use in pregnancy and while breastfeeding, use in immunocompromised patients, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders), use in patients with autoimmune or inflammatory disorders, interaction with other vaccines, and long-term safety constitute missing information. Routine risk minimisation measures and routine, as well as additional, pharmacovigilance activities are in place. There are no additional risk minimisation measures.

A signal of sensorineural hearing loss was validated during the reporting interval following a health authority request (Therapeutic Goods Administration, Australia) on 15 June 2023. The signal was refuted following assessment, shortly after the DLP of this PSUR. Besides, the MAH reviewed supplementary information for the signals of diarrhoea, dyspnoea and tinnitus, and closed these signals shortly after the DLP. Further, rechallenge data on the previously refuted safety signal of menstrual disorders in association with the administration of Nuvaxovid was analysed and this signal was closed, too. Following an EMA inspection in January 2023, L2B case information was downloaded for previously validated and non-validated signals. This information did not change the disposition of the signal status. An update to the signal evaluation report (SER) of myocarditis and pericarditis was generated with the correct date of

validation. Cumulatively, validated signals of anaphylaxis, paraesthesia, myocarditis and pericarditis and tinnitus were confirmed and the CCDS was updated accordingly. Validated and previously evaluated signals of chest pain/chest discomfort, dizziness, encephalitis, encephalomyelitis, menstrual disorders, tachycardia/other rhythm disorders, syncope, acute coronary syndrome associated with hypersensitivity, diarrhoea and dyspnoea were refuted and closed. The MAH states that it will continue to monitor these issues as part of routine surveillance.

The MAH's evaluation of the signals of menstrual disorders, diarrhoea, dyspnoea and sensorineural hearing loss is considered acceptable. With regard to the signal of tinnitus, the PRAC rapporteur is of the opinion that there is currently insufficient evidence to suggest a causal relationship. If, as the MAH notes, tinnitus has been reported in a pattern consistent with typically associated stress or anxiety-related vaccination reactions, tinnitus would have to be labelled for all products within the class. Regarding vaccines against COVID-19, this is so far only the case for Vaxzevria and Jcovden. However, the topic can be discussed controversially and it's at the MAH's discretion to include tinnitus in the product information.

Post authorisation, the MAH states having received a cumulative total of 4,619 spontaneous individual case safety reports (ICSRs, thereof 808 follow-ups), reporting 16,710 adverse events (AEs, thereof 2,491 serious). During the 6-month reporting interval, there were 1,679 ICSRs (thereof 92 follow-ups) with 5,089 AEs (thereof 800 serious). According to PSUR Appendix 5, 795 (32%) of 2,485 spontaneously reported serious adverse reactions (ARs) were reported during the reporting interval, and 4,169 (30%) of 14,091 non-serious ARs. This proportion is high as only 11% of all doses (estimated 335,128 out of 2,986,711) were administered during the reporting interval. The MAH attributes this apparent disproportionality to delayed reports from Korea, from where 1,111 (out of the total of 1,679) ICSRs were entered into the global safety database during the reporting interval; on 03 January 2023 and on 02 May 2023, the MAH received AE data up to 16 June 2022 and 31 December 2022, respectively.

The above (new) information on efficacy included in this PSUR does not modify previous assessments.

Based on the assessment of the data presented in this PSUR, the benefit-risk balance of Nuvaxovid remains unchanged in its authorised indications. No change of the PSUR frequency is proposed.

3. Recommendations

Based on the PRAC 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) remains unchanged and therefore recommends the maintenance of the marketing authorisations.

4. Issues to be addressed in the next PSUR

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

1. Events of tinnitus should continue to be monitored and reported on in the next PSUR(s).

4 PSUR frequency

☒ No changes to the PSUR frequency

The current 6-month frequency for the submission of PSURs should remain unchanged.

Annex: updated PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH submits its 3rd periodic safety update report (PSUR) for COVID-19 vaccine (recombinant, adjuvanted), dispersion for injection (Nuvaxovid, NVX-CoV2373), with the active substance SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda*. The international birth date (IBD), as well as the European Union (EU) reference date (EURD), of Nuvaxovid is 20 December 2021, when the vaccine was granted conditional marketing authorisation by the European Medicines Agency (EMA). This PSUR covers the interval between 20 December 2022 and 19 June 2023, with the data lock point (DLP) 19 June 2023.

Nuvaxovid is a recombinant, adjuvanted protein vaccine indicated for the active immunisation to prevent Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). It contains a purified full-length SARS-CoV-2 recombinant (r) Spike (S) protein that is stabilised in its prefusion conformation and the saponin-based Matrix-M™ adjuvant. The vaccine is authorised as a two-dose primary series and as a booster in individuals 12 years and older, in India as Covovax for individuals 7 years and older. It is a dispersion for intramuscular injection and supplied as a multi-dose vial of 10 doses or 5 doses of 0.5 mL each. On dose contains 5 µg of the recombinant SARS-CoV-2 S protein and 50 µg of the Matrix-M adjuvant.

In its cover letter, the MAH addresses comments from the PRAC assessment reports on the 2nd PSUR (interval 20 June 2022 to 19 December 2022) and the 2nd bimonthly (9th) summary safety report (SSR, interval 16 November 2022 to 15 January 2023). In addition, the MAH points out that "in response to the EMA inspection finding (MA16) and related Corrective and Preventive Actions concerning signal validation and evaluation performed prior to the adoption of a formal Level 2B (L2B) download process", it has "included within this report retrospective reviews of non-validated signals and validated signals". According to the MAH, "the information […] did not change the initial review findings".

The MAH notes that there is an ongoing label variation to the EU product information for boosting in adolescents that was submitted on 24 February 2023. Besides, a submission is planned on 15 August 2023 for the new strain change that will impact the label. The MAH does not propose any further changes to the product information. However, it mentions that the company core data sheet (CCDS) version 7.0 already reflects tinnitus as an undesirable effect in post-marketing experience.

1.2. Worldwide marketing authorisation status

Under the invented names Nuvaxovid and Covovax, the vaccine has been authorised in several countries (first on 31 October 2021 in Indonesia [Covovax]), in the EU region (20 December 2021) and by the World Health Organisation (WHO) for active immunisation to prevent COVID-19 caused by SARS-CoV-2 (PSUR pp. 208-212, Appendix 3, Table 35). Nuvaxovid is approved as a primary series and as a booster vaccine in individuals 12 years and older. In India, Covovax is additionally authorised as a primary series vaccine for individuals 7 years and older.

Table 1: Invented names and countries/region of authorisation (adapted from PSUR pp. 208-212, Appendix 3, Table 35). UK, United Kingdom; USA, United States of America; WHO, World Health Organisation.

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

Rapporteur assessment comment:

During the reporting interval, authorisations were expanded in (alphabetical order) India, Japan, Singapore, South Korea and Taiwan.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

The MAH indicates a Class II level recall on 28 April 2023 of batch 4302MF031 (3,236,200 doses) distributed solely to the Australian market. According to the MAH, an out of specification result was confirmed on investigation at 69 to 78% against a specification of 81 to 85%. The MAH states that no other actions were taken for safety reasons during the reporting interval.

Rapporteur assessment comment:

With the exception of the recall, which was preceded by a notification from the Australian Therapeutic Goods Administration (TGA), the MAH does not report any actions for safety reasons.

1.3.2. Changes to reference safety information

The reference safety information (RSI) in effect at the beginning of the reporting interval was the company core data sheet (CCDS) version 6.0, effective date 10 August 2022. The MAH notes that during the reporting interval, the CCDS was updated to version 7.0 (effective date 02 February 2023) with the following safety-related changes:

- Section 4.8 (undesirable effects) was updated with the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) tinnitus in the system organ class (SOC) of ear and labyrinth disorders from post-marketing experience.
- Sections 4.2, 4.8 and 5.1 (dosing and method of administration, undesirable effects and pharmacodynamic properties) were updated with information in support of adolescent booster dosing.

Besides, section 6.5 (nature and contents of container) was updated to include additional drug product presentation (5-dose vial).

The MAH states that CCDS version 7.0 was in effect at the end of the reporting interval and was used to assess the expectedness of reported adverse events (AEs).

Rapporteur assessment comment:

The MAH does not make any proposals in terms of new safety information and key risk minimisation recommendations. Its wording indicates that the tinnitus labelling update has been submitted to EMA but has not yet been approved (PSUR p. 28, section 4.1).

1.3.3. Estimated exposure and use patterns

Exposure in clinical trials

During the reporting interval, six clinical trials of SARS-CoV-2 rS were ongoing (2019nCoV-101 Part 2, 2019nCoV-301, 2019nCoV-311, 2019nCoV-312, 2019nCoV-503, 2019nCoV-505) and three clinical trials were completed (2019nCoV-302, 2019nCoV-307 and 2019nCoV-501).

Cumulatively, out of 59,691 participants in the clinical development program for the vaccine, 47,395 participants were exposed to SARS-CoV-2 rS, 8,460 participants were exposed to placebo and 3,836 participants were exposed to blinded treatment (2,265 participants in the 2019nCoV-503 study received either SARS-CoV-2 rS or placebo and 1,571 participants in the 2019nCoV-CIC-E-201 study received either SARS-CoV-2 rS or COVID-19 and Influenza Combination [CIC] vaccine or quadrivalent hemagglutinin nanoparticle influenza vaccine [qNIV] or licensed influenza vaccines [Fluzone™ high dose or FLUAD™]).

Table 2: Cumulative exposure stratified by age, sex and treatment (PSUR p. 31, Table 4).

Age Range [a]	Male				Female				Grand Total
	SARS-CoV-2 rS	Placebo	Blinded *	ICC	SARS-CoV-2 rS	Placebo	Blinded *	ICC	
6 months – < 24 months	0	0	54	0	0	0	46	0	100
2 – < 6 Years	0	0	470	0	0	0	435	0	905
6 – < 12 Years	0	0	633	0	0	0	627	0	1,260
12 – < 18 Years	1,131	41	0	0	1,026	34	0	0	2,232
18 – 34 Years	6,680	750	0	0	5,758	687	0	0	13,875
35 – 50 Years	7,320	967	16	15	7,015	971	21	22	16,347
51 – 65 Years	6,559	1,409	406	155	6,602	1,470	536	277	17,414
> 65 Years	2,833	1,176	279	42	2,471	955	313	47	8,116
Total	24,523	4,343	1,858	212	22,872	4,117	1,978	346	60,249

[a] Excludes participant data from 2019nCoV-312 study as the participants are a subset of 2019nCoV-307 study
* Includes blinded data from 2019nCoV-503 and 2019nCoV-CIC-E-201 studies

Rapporteur assessment comment:

As requested in the assessment of the last PSUR, the MAH now presents data on age and sex of subjects in clinical trials. This is endorsed. According to Tables 4 and 5 (PSUR pp. 31-32), predominantly white adults were included in clinical trials with the vaccine. The sex distribution of the participants is quite balanced.

Exposure from post-authorisation experience

During the reporting interval, 314,830 NVX-CoV2373 doses were administered across Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, United Kingdom (UK) and the United States of America (USA) and 14,414 Covovax doses were administered in India. A total of 9,790,300 NVX-CoV2373 doses (9,784,700 NVX-CoV2373 and 5,600 Covovax doses) were distributed globally.

Cumulatively, 2,872,381 NVX-CoV2373 doses were administered in Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, UK and the USA, and 41,762 Covovax doses were administered in India. A total of 112,787,170 NVX-CoV2373 doses (103,452,920 NVX-CoV2373 and 9,334,250 Covovax doses) were distributed globally.

Table 3: Interval and cumulative estimated exposure data (administered) from post-authorisation experience (PSUR pp. 35-36, Table 7).

Dose	Actual Doses Administered [a]	Adjusted doses including re-allocated doses (from unknown dose number or unknown vaccine) [b]	Calculated Doses Administered [c]	Total Estimated Doses Administered [d]
Interval				
First Dose	45,815	47,369	38	47,407
Second Dose	49,865	51,713	60	51,773
Booster Dose	233,473	235,459	397	235,856
Unknown Dose Number	0	0	0	0
Interval Total [e]	329,244	334,633	495	335,128
Cumulative				
First Dose	643,150	682,106	38	682,144
Second Dose	505,602	530,570	60	530,630
Booster Dose	1,762,617	1,770,773	397	1,771,170
Unknown Dose Number	9	0	0	0
Cumulative Total [e]	2,914,143	2,986,216	495	2,986,711

NOTE: Data sources and cut off dates are presented in Table 6 above. The total number of doses administered column may not add to the number of individuals as individuals may receive more than 3 doses.

[a] 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 6 for the list of countries with administration data.

[b] Column represents administration data re-allocated to first, second and booster dose only (refer to calculations above Table 7). 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 6 are presented in this column. For a list of countries for which this re-allocation was applied, refer to text above Table 7

[c] 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 7 and in Appendix 10.

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

[e] The interval and cumulative total is not consistent with the sum of the individual dosing because part of the data presented represents the 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.

According to PSUR Table 9 (p. 37), when known, most doses were administered to elderly subjects.

Table 4: Interval and cumulative administration data by age group from post-authorisation experience (PSUR p. 37, Table 9).

Total Doses Actually Administered [a,b,c,d]			
Dose	**Paediatrics**	**Adults**	**Elderly**
Interval			
First Dose	6	404	927
Second Dose	38	590	1,250
Third/Booster Dose	21	1,982	5,702
Interval Total	65	2,976	7,879
Cumulative			
First Dose	160	153,250	22,149
Second Dose	162	111,944	18,107
Third/Booster Dose	180	118,206	46,209
Cumulative Total	502	383,400	86,465

[a] 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 6 above, with the exception of New Zealand and Australia as age stratified data is only available until 31-Dec-2022 and 21-Dec-2022 respectively.

[b] Some countries in EU did not provide age categories consistently as per European Center for Disease Prevention and Control (ECDC) data, so this table does not cover all doses from ECDC data.

c Australia and New Zealand had administration data in only adolescent and elderly age groups. Japan had administration data for only elderly age groups (65+ years).

[d] Of note, age group stratification is not standardised across countries and regions. Age groups for the EU, Australia, and New Zealand are as follows: Paediatric < 8 years; adults 18 – 69 years; elderly 70 + years. Age stratification for Switzerland is as follows: Paediatric- ≤ 19 years; adults: 20 – 69 years; elderly 70 + years. Japan classifies elderly as 65+ years

Numbers of doses administered and distributed are tabulated by country/region.

Table 5: Interval exposure data (administered and distributed) from post-authorisation experience presented by region/license partner (PSUR p. 38, Table 10). a, data presented as recorded; b, Nuvaxovid; c, Covovax; LP, license partner.

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Interval (20-Dec-2022 – 19-Jun-2023)		
Australia (Biocelect Pty Ltd) [b]	23,451	2,988,500
Canada (NVX) [b]	4,446	Not available
EU (NVX) [b]	5,545	131,100
Germany (NVX) [b]	2,850	3,000,000
India (SIIPL) [c]	14,414	5,600
Indonesia (SIIPL) [c]	Not available	Not available
Israel (Medicalix/Freyr) [b]	15	1,000,000
Japan (Takeda) [b]	49,691	Not available
New Zealand (Biocelect New Zealand Ltd.) [b]	828	252,000
Singapore (PharmaEng Technology Pte Ltd) [b]	22,800	90,000
South Korea (SK Bioscience) [b]	50,931	0
Switzerland (NVX) [b]	459	24,400
Taiwan (NVX) [b]	130,001	797,200
Thailand (SIIPL) [c]	Not available	Not available
UK (NVX) [b]	589	Not available
USA (NVX) [b]	23,224	1,501,500
Nuvaxovid Total	314,830	9,784,700
COVOVAX Total	14,414	5,600
Interval Total	329,244	9,790,300

Table 6: Cumulative exposure data (administered and distributed) from post-authorisation experience presented by region/license partner (PSUR p. 39, Table 10). a, data presented as recorded; b, Nuvaxovid; c, Covovax; LP, license partner.

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Cumulative		
Australia (Biocelect Pty Ltd.) [b]	259,000	24,224,800
Canada (NVX) [b]	32,883	9,724,000
EU (NVX) [b]	351,400	22,335,070
Germany (NVX) [b]	160,154	23,404,690
India (SIIPL) [c]	41,762	126,250
Indonesia (SIIPL) [c]	Not Available	9,008,000
Israel (Medicalix/Freyr) [b]	43	1,535,100
Japan (Takeda) [b]	322,886	8,238,590
New Zealand (Biocelect New Zealand Ltd.) [b]	7,867	2,283,800
Singapore (PharmaEng Technology Pte Ltd) [b]	40,873	705,000
South Korea (SK Bioscience) [b]	971,309	2,932,470
Switzerland (NVX) [b]	3,013	526,400
Taiwan (NVX) [b]	632,494	1,805,200
Thailand (SIIPL) [c]	Not Available	200,000
UK (NVX) [b]	1,264	1,000,000
USA (NVX) [b]	89,195	4,737,800
Nuvaxovid Total	2,872,381	103,452,920
COVOVAX Total	41,762	9,334,250
Cumulative Total	2,914,143	112,787,170

Rapporteur assessment comment:

The MAH estimates that approximately 11% of all doses cumulatively administered (335,128 out of 2,986,711 doses) were applied during the reporting interval, particularly as booster doses (235,856 out of 1,771,170 booster doses, i.e. 13% of all cumulative booster doses). According to Table 10 of the PSUR, during the reporting interval, most doses were administered in Taiwan, South Korea and Japan. Cumulatively, the vaccine was most frequently applied in South Korea, Taiwan, and the EU. Considerably fewer doses were administered during this reporting interval than in the previous one (335,128 and 1,380,949 doses, respectively). There is still a marked discrepancy between the number of vaccine doses delivered and those administered.

1.3.4. Data in summary tabulations

In Appendix 4 of its 3rd PSUR, the MAH presents cumulative summary tabulations of serious adverse events (SAEs) from company-sponsored interventional clinical trials from the development international birth date (DIBD, 23 April 2020) to the DLP (19 June 2023) of the PSUR. The MAH notes that due to the complexity of cross-over study design, data are analysed across the clinical development program by study time period, such as pre-crossover, post-crossover and booster, time interval to event onset and across multiple doses of active and placebo products.

The MAH summarises the SOCs of the most frequently reported SAEs from studies 2019nCoV-101 (part 1 and part 2), 2019nCoV-301, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311, 2019nCoV-312, 2019nCoV-501, 2019nCoV-503, and 2019nCoV-505. In 2019nCoV-301, the study with the largest number of participants, 29,582 adults and 2,232 adolescents received either SARSCoV-2 rS with Matrix-M adjuvant

or placebo and experienced a total of 2,141 treatment emergent SAEs. The MedDRA SOCs under which the SAEs have been most frequently reported include *Infections and Infestations* (475 PTs), *Cardiac Disorders* (251 PTs) and *Injury, Poisoning and Procedural Complications* (177 PTs).

Post authorisation, the MAH states having received 1,679 spontaneous individual case safety reports (ICSRs) during the 6-month reporting interval (of which 92 ICSRs contained follow-ups), with 5,089 AEs, thereof 601 serious unlisted, 199 serious listed, 1,517 non-serious unlisted, and 2,772 non-serious listed. Cumulatively, 4,619 spontaneous ICSRs have been received (of which 808 were follow-ups), reporting 16,710 AEs, thereof 2,491 serious. A total of 19 fatal ICSRs were reported during the 6-month interval, and 28 fatal ICSRs cumulatively. The MAH notes that, on 03 January 2023 and on 02 May 2023, it received AE data up to 16 June 2022 and 31 December 2023, respectively, from South Korea, and that these ICSRs were entered into the Nuvaxovid global safety database.

According to the MAH, up-to-date individual case-level information from South Korea is not available for downloading into the Nuvaxovid safety database. This is why the MAH reviews the aggregated data separately and presents it in a distinct section of the PSUR (section 6.3.1). As of 21 May 2023, a cumulative total of 971,309 Nuvaxovid doses were administered in South Korea, and 1,279 AEs were reported. The five most commonly reported symptoms (PSUR pp. 43-44, Table 11) included myalgia (n = 274 cases), headache (n = 253), dizziness (n = 179), chest pain (n = 171), and allergic reaction (n = 169). Four cases of myocarditis were identified (two males and two females, age range 20-59 years). A review of suspected anaphylaxis cases between 26 February 2021 and 28 April 2023 yielded 7 cases, 6 of which had a causal relationship with the administration of Nuvaxovid, according to the report of the Korean Disease Control and Prevention Agency (KDCA). 13 cases described a fatal outcome. Autopsy was not performed in any case. The time from vaccination to death was at ≥ 3 days in 11 cases, and most individuals were ≥ 60 years old (60-69 years, n = 3; 70-79 years, n = 3; ≥ 80 years, n = 5). The MAH concludes that the aggregate data from South Korea is consistent with the known safety profile of Nuvaxovid, and that it did not identify new signals.

Rapporteur assessment comment:

Appendix 4 lists MedDRA SOCs and PTs of SAEs observed in clinical trials, separately by study. The MAH addresses the assessment comment on the presentation of summary tabulations in the last PSUR, and points out challenges in the attribution of events from studies with cross-over design.

Appendix 5 provides summary tabulations of serious and non-serious adverse reactions from post-authorisation data sources. Of a cumulative total of 16,576 spontaneously reported events, 4,774 are listed under the SOC *General disorders and administration site conditions*, 2,900 under the SOC *Nervous system disorders*, 1,817 under the SOC *Musculoskeletal and connective tissue disorders*, 1,136 under the SOC *Gastrointestinal disorders*, 993 under the SOC *Skin and subcutaneous tissue disorders*, 778 under the SOC *Respiratory, thoracic and mediastinal disorders*, 670 under the SOC *Cardiac disorders*, 506 under the SOC *Immune system disorders*, 487 under the SOC *Injury, poisoning and procedural complications*, and 429 under the SOC *Infections and infestations*. It is noted that 22 of a cumulative 24 serious anaphylactoid reactions were reported in the reporting interval, 19/19 non-serious generalised oedema AEs, as well as 5/16 serious and 373/396 non-serious hypersensitivity AEs.

Although substantially fewer doses were administered during this reporting interval (2nd PSUR, 20 June 2022 to 19 December 2022, 1,380,949 doses; 3rd PSUR, 20 December 2022 to 19 June 2023, 335,128 doses), there were comparatively more ICSRs (2nd PSUR, 1,363 ICSRs reporting 4,950 AEs; 3rd PSUR, 1,679 ICSR reporting 5,089 AEs). Of 2,485 spontaneously reported SAEs, 795 (32%) were reported during the reporting interval, and 4,169 (30%) of 14,091 non-serious AEs. This proportion is high as only 11% of all doses (335,128 out of 2,986,711) were administered during the reporting interval. The discrepancy might partially be due to the fact that AEs from South Korea have now been included in the database. However,

this is not entirely clear from the information in the PSUR, and also in South Korea, significantly fewer doses were administered in the reporting interval of this PSUR (2nd PSUR, 345,993 doses; 3rd PSUR, 50,931 doses). The MAH is kindly asked to comment on the disproportionately high number of AEs in the reporting interval. In addition, it should explain why the text reports a cumulative total of 16,710 AEs (PSUR p. 42) and Appendix 5 a cumulative total of 16,576 AEs (PSUR p. 335). Also, among the SAEs reported post-marketing, at least one seems to be missing in Appendix 5.

Anaphylaxis is mentioned in section 4.4 of the summary of product characteristics (SmPC) and listed in section 4.8, with the frequency *not known*.

From the information provided, no new important safety information is identified.

1.3.5. Findings from clinical trials and other sources

Completed clinical trials

The MAH states that during the reporting interval, three clinical trials were completed (2019nCoV-302, 2019nCoV-307, and 2019nCoV-501).

Study **2019nCoV-302**, a phase 3, multicentre, randomised, observer-blinded, placebo-controlled crossover design study, evaluated the efficacy, safety, and immunogenicity of a two-dose regimen of NVX-CoV2373 administered 21 days apart in 15,187 adult participants 18 to 84 years of age across 33 sites in the UK. The vaccine efficacy to prevent symptomatic mild, moderate, or severe COVID-19 in serologically negative (to SARS-CoV-2) adult participants at baseline was 82.6% (95% confidence interval [CI]: 72.9-88.8%). Over the course of the surveillance period, vaccine efficacy decreased. According to the MAH, the majority of participants in the NVX-CoV2373 group reported mild, grade 1 events following the first vaccination and grade 1 or grade 2 events following the second vaccination. No new safety signals were detected during the initial vaccination period nor in the crossover period.

The phase 3 study **2019nCoV-307** evaluated the immunogenicity and safety of three different manufacturing lots of NVX-CoV2373 administered across 31 sites in the USA to adults (18 to 49 years) who were vaccinated against SARS-CoV-2 (primary series with or without booster) at least six months prior to this study. 847 adult subjects were evaluated for immunogenicity and 865 subjects for safety. According to the MAH, the primary immunogenicity endpoint was achieved as equivalence was demonstrated for all pairs of NVX-CoV2373 lots as the 95% CIs of immunoglobulin G (IgG) geometric mean enzyme-linked immunosorbent assay (ELISA) units (GMEUs) specific for the SARS-CoV-2 S protein (Wuhan) were within the pre-specified equivalence range of 0.67 to 1.5. The MAH states that safety across the three lots was comparable and consistent with the known safety profile of NVX-CoV2373.

Study **2019nCoV-501**, an observer-blinded, placebo-controlled trial investigating the efficacy, safety, and immunogenicity at month 12 of a two-dose regimen of NVX-CoV2373 administered 21 days apart in both primary vaccination and crossover/booster vaccination periods in healthy human immunodeficiency virus (HIV)-negative South African adult participants and medically stable people living with HIV (PLWH) South African participants, evaluated 4,408 South African healthy participants (≥ 18 to < 85 years) and 245 medically stable PLWH participants (≥ 18 to < 65 years). The vaccine efficacy in prevention of symptomatic mild, moderate, or severe COVID-19 in participants seronegative (to SARS-CoV-2) at baseline was 48.6% (95% CI: 28.4-63.1). The MAH notes that local and systemic reactogenicity were primarily mild to moderate and transient and higher in the NVX-CoV2373 group. Serious adverse events were rare in both groups, and the 20 deaths observed (10 each in the NVX-CoV2373-to-booster group and in the placebo-to-NVX-CoV2373 group) were assessed as not related to trial vaccine.

Ongoing clinical trials

As of the DLP (19 June 2023) for this reporting interval, three clinical trials were ongoing: study

2019nCoV-101 Part 2, study 2019nCoV-301, and study 2019nCoV-311 Parts 1 and 2. The MAH states that no unexpected new safety information has emerged from these ongoing studies during the reporting interval.

Long-term follow-up

The MAH states that all 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. According to the MAH, no new safety information became available from long-term follow-up in company-sponsored clinical trials.

Other therapeutic use of medicinal product

During the reporting interval, one compassionate use study was completed in South Africa for healthcare workers, as part of the 2019nCoV-501 study. A total of 99 healthcare workers were enrolled and 87 of them completed the study. According to the MAH, no clinically relevant safety information was reported.

New safety data related to fixed combination therapies

During the reporting interval, the phase 2, randomised, observer-blind study 2019nCoV-CIC-E-201 to evaluate the safety and immunogenicity of a fixed combination of quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy participants ≥ 50 to ≤ 80 years of age is ongoing. As of the DLP, 1,571 participants were randomised and no significant safety findings were observed.

Non-interventional studies

The MAH states that no significant safety or efficacy findings that would have an impact on the benefit-risk profile of NVX-CoV2373 were reported from any non-interventional studies.

Other clinical trials

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

Medication errors

In its global vaccine safety database, the MAH retrieved 84 ICSRs for the interval (79 initial and 5 follow-ups). The 228 cumulative ICSRs included 290 medication error related AEs, thereof one serious and 289 non-serious. The most common PTs reported were "expired product administered" (n = 37), "inappropriate schedule of product administration" (n = 30), "incomplete course of vaccination" (n = 26), "interchange of vaccine products" (n = 26), "vaccination error" (n = 21), "product administration error" (n = 20), "product administered to patient of inappropriate age" (n = 20), "incorrect product formulation administered" (n = 19), "incorrect dose administered" (n = 18), "product storage error" (n = 17), "wrong product administered" (n = 16), and "product dose omission issue" (n = 10). The MAH's assessment did not reveal any particular trend or new potential safety issues.

Non-clinical data

During the reporting interval, there were five completed and 15 ongoing non-clinical studies for SARS-CoV-2 rS. Table 14, pp. 56-61, summarises these 20 non-clinical studies. 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

During the reporting interval, the MAH conducted weekly literature searches and reviewed a total of 194 publications. Of these, according to the MAH, 35 publications presented new, important information and are briefly outlined. The MAH concludes that its literature review did not identify any significant safety

findings that would impact the overall benefit-risk balance of NVX-CoV2373.

Other periodic reports

Table 15, p. 73, lists periodic SSRs submitted to health authorities. The MAH states that it did not identify any new significant safety-related issues from these reports.

Rapporteur assessment comment: The information provided does not reveal emerging safety issues.

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 notes that no late breaking information with reference to Nuvaxovid's safety, efficacy and effectiveness has been received after the DLP of this periodic benefit-risk evaluation report (PBRER).

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 7: Summary of safety concerns at the beginning of the reporting interval (EU RMP version 2.1, dated 01 September 2022). The MAH notes that during the reporting period, the EU RMP was updated to version 3.1, dated 06 February, with no changes to the list of safety concerns.

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

2.2. Signal evaluation

The MAH notes that a signal of sensorineural hearing loss was validated during the reporting interval following a health authority request (TGA) received on 15 June 2023. The signal was refuted following assessment, shortly after DLP of this report (on 30 July 2023). Besides, the MAH reviewed supplementary information for the signals of diarrhoea, dyspnoea and tinnitus. According to the MAH, no changes were made to the previous disposition of these signals after the review and the signals were closed shortly

after the DLP. Further, rechallenge data on the previously refuted safety signal of menstrual disorders in association with the administration of Nuvaxovid was analysed. No changes were made to the previous disposition of this signal after the review, and the signal was closed.

For the cumulative period up to 19 June 2023, signals of anaphylaxis, myocarditis and pericarditis, paraesthesia/hypoaesthesia and tinnitus have been confirmed. The CCDS has been updated to include anaphylaxis in section 4.4 (special warnings and precautions for use) and paraesthesia/hypoaesthesia and tinnitus in section 4.8 (undesirable effects). Besides, the CCDS was updated to include myocarditis and pericarditis in sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects).

The MAH notes that, following an EMA inspection in January 2023, retrospective Level 2B case information was downloaded from EudraVigilance for the previously validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus and non-validated signals of angina pectoris, hypertension, herpes zoster and oral herpes. According to the MAH, no significant information was received in the L2B downloads that altered the previous disposition of these signals. However, an updated signal evaluation report (SER) was generated after the DLP for the signal of myocarditis and pericarditis with the correct date of validation.

*Table 8: Tabular overview of signals: new, ongoing or closed, cumulatively (PSUR pp. 336-342, Appendix 6, Table 36) and during the reporting interval (20 December 2022 to 19 June 2023; on orange background). HA, health authority; PRAC, pharmacovigilance risk assessment committee; RMP, risk management plan; SER, signal evaluation report; SmPC, summary of product characteristics; SSR, summary safety report; * signal closed after the DLP.*

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Anaphylaxis	18 May 2022	Closed	27 June 2022	HA query (TGA/EMA)	HA request	Provided in SER submitted with SSR 05	Anaphylaxis local label updated for Australia. Added to sections 4.4 and 4.8 of the CCDS V5.0. A safety variation was approved on 06 September 2022.
Myopericarditis, myocarditis and pericarditis	17 May 2022	Closed	03 August 2022	HA query (TGA/EMA)	HA request	Provided in SER submitted with SSR 05	Added to sections 4.4 4.8 of the CCDS V6.0. Reclassified myocarditis and/or pericarditis to an important identified risk in RMP. A safety variation was approved on 25 October 2022 for the SmPC. Pericarditis local label updated for Australia.
Paraesthesia	27 May 2022	Closed	27 June 2022	HA query (TGA/EMA)	HA request	Provided in SER submitted with SSR 05	Paraesthesia local label updated for Australia. Added to section 4.8 of the CCDS V5.0. A safety variation was submitted to EMA by NVX for approval of SmPC. This variation was approved on 06 September 2022.
Chest Pain/Chest Discomfort	15 June 2022	Closed	09 August 2022	Health Canada request	HA request	Provided in SER submitted with SSR 06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
	29 August 2022	Closed	12 September 2022	PRAC request	HA request	Provided in the addendum to the SER submitted with SSR 07	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Dizziness	15 June 2022	Closed	05 August 2022	Health Canada request	HA request	Provided in SER submitted with SSR 06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	29 August 2022	Closed	12 September 2022	PRAC request	HA request	Provided in the addendum to the SER submitted with SSR 07	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Encephalitis/ Encephalomyelitis	16 June 2022	Closed	05 August 2022	KDCA Query	HA request	Provided in SER submitted with SSR 06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Menstrual disorders	27 June 2022	Closed	05 August 2022	PRAC request	HA request	Provided in SER submitted with SSR 06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	29 August 2022	Closed	12 September 2022	PRAC request	HA request	Provided in the addendum to the SER submitted with SSR 07	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	28 December 2022	Closed	18 January 2023	PRAC request	HA request	Addendum for menstrual disorders with rechallenge is provided in second bimonthly SSR and in Appendix 20	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Tachycardia and other rhythm disorders	27 June 2022	Closed	09 August 2022	PRAC request	HA request	Provided in SER submitted with SSR 06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	29 August 2022	Closed	12 September 2022	PRAC request	HA request	Provided in the addendum to the SER submitted with SSR 07	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Acute coronary syndrome associated with hypersensitivity	27 July 2022	Closed	12 September 2022	PMDA request	HA request	Provided in SER submitted with SSR 07	The signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
Syncope	25 July 2022	Closed	12 September 2022	PRAC request	HA request	Provided in SER submitted with SSR 07	Syncope is adequately labelled in SmPC section 4.4. Continue routine surveillance.
Diarrhoea	14 November	Closed	18 January	PRAC request	HA request	Provided in SER	This signal was refuted based on current available

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
	2022		2023			submitted with bi-monthly SSR 02 and SSR 13	data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	07 March 2023	Closed*	06 July 2023	PRAC request	HA request	Provided in SER addendum	SER addendum submitted in Appendix 21
Dyspnoea	14 November 2022	Closed	18 January 2023	PRAC request	HA request	Provided in SER submitted with bi-monthly SSR 02 and SSR 13	This signal was refuted based on current available data from clinical trials and the post-authorisation setting. Continue routine surveillance.
	07 March 2023	Closed*	17 July 2023	PRAC request	HA request	Provided in SER addendum	SER addendum submitted in Appendix 22
Tinnitus	14 November 2022	Closed	18 January 2023	PRAC request	HA request	Provided in SER submitted with bi-monthly SSR 02 and SSR 13	The signal of tinnitus was confirmed as a nonimportant risk based on the post-marketing reports and incorporation of tinnitus in the CCDS was recommended. Australian Product Information V7: updated section 4.8; V7 25 January 2023 CCDS V 7.0 was approved by the Global Labeling Committee to include Tinnitus under section 4.8 on 02 February 2023.
	07 March 2023	Closed*	18 July 2023	PRAC request	HA request	Provided in SER addendum	SER addendum submitted in Appendix 23
Sensineural hearing loss	15 June 2023	Closed*	30 July 2023	HA query (TGA)	HA request	Provided in SER	SER submitted in Appendix 24

The MAH mentions two requests from SwissMedic, to discuss tachycardia and rhythm disorders and menstrual disorders. It did not identify a safety signal.

Diarrhoea. As requested in the assessment report on the 2nd bimonthly (9th) SSR, the MAH repeated its database search using the MedDRA high level term (HLT) diarrhoea (excl infective) and the DLP of the original SER (16 November 2022). The MAH states that it did not identify any new cases by the expanded search strategy und its signal assessment remains unchanged at refuted (SER addendum, PSUR Appendix 21).

Dyspnoea. Following the receipt of the assessment report on the 2nd bimonthly (9th) SSR, the MAH expanded its search strategy for the additional PTs dyspnoea at rest, orthopnoea, laryngeal dyspnoea, and use of accessory respiratory muscles in the global safety database, as well as dyspnoea exertional in the clinical trial database. The MAH states that it did not identify any additional ICSRs by the added search terms. A SER addendum is presented in Appendix 22 of the PSUR. The MAH concludes that a causal association between dyspnoea as a unique medical concept and Nuvaxovid remains not supported and the signal of dyspnoea remains refuted.

Tinnitus. The MAH presents an addendum SER in Appendix 23 of the PSUR. It states that tinnitus remained to be a confirmed signal and CCDS version 7.0 already reflects tinnitus as an undesirable effect in post-marketing experience. No further actions are planned as of DLP.

Sensorineural hearing loss. The MAH comprehensively reviewed relevant safety data from clinical trials and the post-authorisation safety database. The SER is presented in Appendix 24 of the PSUR. No imbalance related to sensorineural hearing loss was identified from the clinical trial data. 19 ICSRs were retrieved in the post-authorisation safety database (13 females, 6 males age range 22-73 years, median age 48 years). Positive rechallenge of sudden hearing loss was noted in two reports, unilateral hearing loss in seven reports, and bilateral hearing loss in three reports. Time to onset (TTO) was 0-10 days in most cases (n = 11, 58%). 10 ICSRs had confounders including evidence of concurrent infection, underlying autoimmune disease, tachycardia possibly associated with stress or anxiety, and history of traumatic deafness. The overall and age-stratified O/E ratios were significantly lower than 1. The MAH concludes that the current evidence does not support a causal association between Nuvaxovid and sensorineural hearing loss.

Besides, the global vaccine safety database was queried for **adverse events of special interest (AESIs)** for the cumulative period up to the DLP (19 June 2023) according to prespecified search strategies. All retrieved ICSRs were reviewed individually and in aggregate and cumulative observed versus expected (O/E) analyses were performed. The MAH lists the following AESIs:

- Acute Disseminated Encephalomyelitis
- 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
- 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
- Venous Thromboembolism

The MAH did not retrieve any ICSRs for the AESIs acute disseminated encephalomyelitis, foetal growth restriction, gestational diabetes, Kawasaki's disease, major congenital anomalies, maternal death, microcephaly, narcolepsy, neonatal death, preterm birth, stillbirth, sudden death, and transverse myelitis.

Anaphylaxis. A signal of anaphylaxis was validated on 18 May 2022 and confirmed on 27 June 2022. The CCDS was updated to include anaphylaxis in sections 4.4 and 4.8. 26 ICSRs were retrieved for the interval (24 initial and 2 follow-ups) and 69 ICSRs cumulatively, involving 59 females and 10 males with, when reported, a median age of 40.5 years (range, 17-75 years). A total of 81 AEs were reported cumulatively, most of which were coded to the PT anaphylactic reaction (n = 42, 51.8%; anaphylactoid reaction, n = 24; anaphylactic shock, n = 7; circulatory collapse, n = 6; shock, n = 1; type I hypersensitivity, n = 1). The crude O/E results showed an increase in the observed rate compared to the expected rate which was statistically significant. O/E results also showed an increase in the observed rate for the 0-1 and 0-2 risk windows.

Table 9: O/E analysis of anaphylaxis with sensitivity analysis for all cumulative AEs (PSUR p. 85, Table 18).

Risk Window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
All Doses			
0 – 1 Day	14.52 (11.21 – 18.51) *	29.04 (22.41 – 37.01) *	58.08 (44.83 – 74.02) *
0 – 2 Days	7.25 (5.59 – 9.24) *	14.49 (11.19 – 18.47) *	28.98 (22.37 – 36.94) *
0 – 7 Days	2.10 (1.63 – 2.67) *	4.20 (3.25 – 5.35) *	8.41 (6.50 – 10.70) *
Dose 1			
0 – 1 Day	8.58 (3.93 – 16.29) *	17.17 (7.86 – 32.58) *	34.34 (15.72 – 65.17) *
0 – 2 Days	4.32 (1.98 – 8.19) *	8.63 (3.95 – 16.38) *	17.26 (7.90 – 32.76) *
0 – 7 Days	1.23 (0.56 – 2.33)	2.46 (1.12 – 4.66) *	4.91 (2.25 – 9.32) *
Dose 2			
0 – 1 Day	7.46 (2.73 – 16.23) *	14.91 (5.47 – 32.46) *	29.82 (10.94 – 64.92) *
0 – 2 Days	3.71 (1.36 – 8.09) *	7.43 (2.72 – 16.17) *	14.86 (5.45 – 32.34) *
0 – 7 Days	1.06 (0.39 – 2.31)	2.12 (0.78 – 4.62)	4.24 (1.56 – 9.24) *
Booster			
0 – 1 Day	7.23 (4.35 – 11.28) *	14.45 (8.70 – 22.57) *	28.90 (17.40 – 45.13) *
0 – 2 Days	3.61 (2.17 – 5.64) *	7.22 (4.35 – 11.27) *	14.44 (8.69 – 22.54) *
0 – 7 Days	1.03 (0.62 – 1.61)	2.06 (1.24 – 3.22) *	4.13 (2.49 – 6.45) *

* Increased and statistically significant O/E results.

Results for all reports stratified by age and sex were statistically significant for the total male group, males 20-49 years, females 0-69 years, and the total female group. Considering the limited availability of demographic information, the MAH concludes that the current available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable. Of the 69 ICSRs for anaphylaxis, 15 cases were adjudicated to Brighton Collaboration (BC) level 1-3 criteria. For these cases, the O/E results showed a statistically significant increase in the observed rate compared to the expected rate for the 0-1-day risk window.

Myocarditis and pericarditis. A signal of myocarditis and pericarditis was validated on 17 May 2022 and confirmed on 03 August 2022. The CCDS was updated to include myocarditis and pericarditis in sections 4.4 and 4.8.

9 ICSRs were retrieved for the interval (8 initial and 1 follow-up) using the narrow search strategy for **myocarditis**. Cumulatively, 28 ICSRs were retrieved (14 females, 14 males, age range 18-83 years when reported, median age 32 years). The 28 cumulative ICSRs included 28 AEs coded to the PTs myocarditis (n = 22) and myopericarditis (n = 6). Results of O/E analysis showed a statistically significant increase in the observed rate compared to the expected rate for all risk windows.

Table 10: O/E analysis of myocarditis with sensitivity analysis for all cumulative AEs (PSUR p. 103, Table 22).

Risk window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
All AEs			
0 – 7 Days	12.76 (7.90 – 19.50)*	25.52 (15.80 – 39.00)*	51.03 (31.59 – 78.01)*
0 – 14 Days	6.99 (4.43 – 10.49)*	13.98 (8.86 – 20.97)*	27.95 (17.72 – 41.94)*
0 – 30 Days	4.00 (2.61 – 5.86)*	8.00 (5.23 – 11.73)*	16.01 (10.45 – 23.45)*
0 – 42 Days	3.03 (1.98 – 4.44)*	6.06 (3.96 – 8.89)*	12.13 (7.92 – 17.77)*
Dose 1			
0 – 7 Days	7.07 (1.46 – 20.68)*	14.15 (2.92 – 41.36)*	28.29 (5.85 – 82.71)*
0 – 14 Days	3.54 (0.73 – 10.34)	7.07 (1.46 – 20.67)*	14.14 (2.92 – 41.34)*
0 – 30 Days	2.36 (0.49 – 6.89)	4.72 (0.97 – 13.79)	9.43 (1.95 – 27.58)*
0 – 42 Days	2.36 (0.49 – 6.89)	4.72 (0.97 – 13.79)	9.43 (1.95 – 27.58)*
Dose 2			
0 – 7 Days	12.51 (3.41 – 32.02)*	25.02 (6.82 – 64.04)*	50.03 (13.63 – 128.08)*
0 – 14 Days	6.25 (1.70 – 16.00)*	12.50 (3.41 – 31.99)*	24.99 (6.81 – 63.98)*
0 – 30 Days	2.92 (0.80 – 7.47)	5.84 (1.59 – 14.95)*	11.68 (3.18 – 29.89)*
0 – 42 Days	2.09 (0.57 – 5.34)	4.17 (1.14 – 10.69)*	8.35 (2.28 – 21.38)*
Booster			
0 – 7 Days	1.11 (0.03 – 6.17)	2.22 (0.07 – 12.35)	4.43 (0.13 – 24.70)
0 – 14 Days	0.55 (0.02 – 3.09)	1.11 (0.03 – 6.18)	2.22 (0.07 – 12.35)
0 – 30 Days	0.26 (<0.01 – 1.44)	0.52 (0.02 – 2.89)	1.04 (0.03 – 5.78)
0 – 42 Days	0.19 (<0.01 – 1.03)	0.37 (0.01 – 2.07)	0.74 (0.02 – 4.14)

* Increased and statistically significant O/E results

During the reporting interval, 8 initial ICSRs were retrieved using the narrow search strategy for **pericarditis**. Cumulatively, 50 ICSRs were retrieved (25 females, 25 males; age range 23-83 years when reported, median age 39 years). The 50 cumulative ICSRs included 50 AEs coded to the PT pericarditis (n = 50). O/E results showed an increased observed rate that was statistically significant for 0-7 and 0-14-day risk windows. Stratified by age and sex and considering the 0-42 days risk window, O/E results showed a statistically significant increase in the observed rate compared to the expected rate in the 20-39-year-old male group.

Table 11: O/E analysis of pericarditis with sensitivity analysis for all cumulative AEs (PSUR pp. 107-108, Table 25).

Risk window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
All AEs			
0 – 7 Days	4.01 (2.88 – 5.44) *	8.02 (5.76 – 10.88) *	16.04 (11.51 – 21.76) *
0 – 14 Days	2.30 (1.69 – 3.06) *	4.60 (3.38 – 6.12) *	9.20 (6.76 – 12.23) *
0 – 30 Days	1.20 (0.89 – 1.59)	2.40 (1.78 – 3.17) *	4.80 (3.55 – 6.35) *
0 – 42 Days	0.92 (0.68 – 1.21)	1.84 (1.37 – 2.43) *	3.68 (2.73 – 4.85) *
Dose 1			
0 – 7 Days	1.32 (0.27 – 3.85)	2.64 (0.54 – 7.71)	5.27 (1.09 – 15.41) *
0 – 14 Days	0.66 (0.14 – 1.93)	1.32 (0.27 – 3.85)	2.64 (0.54 – 7.70)
0 – 30 Days	0.44 (0.09 – 1.28)	0.88 (0.18 – 2.57)	1.76 (0.36 – 5.14)
0 – 42 Days	0.44 (0.09 – 1.28)	0.88 (0.18 – 2.57)	1.76 (0.36 – 5.14)
Dose 2			
0 – 7 Days	0.56 (0.02 – 3.12)	1.12 (0.03 – 6.24)	2.24 (0.07 – 12.47)
0 – 14 Days	0.28 (<0.01 – 1.56)	0.56 (0.02 – 3.12)	1.12 (0.03 – 6.23)
0 – 30 Days	0.26 (0.03 – 0.94) **	0.52 (0.06 – 1.89)	1.05 (0.13 – 3.77)
0 – 42 Days	0.19 (0.02 – 0.67) **	0.37 (0.04 – 1.35)	0.75 (0.09 – 2.70)
Booster			
0 – 7 Days	0.65 (0.18 – 1.66)	1.30 (0.35 – 3.32)	2.60 (0.71 – 6.65)
0 – 14 Days	0.41 (0.13 – 0.95) **	0.81 (0.26 – 1.89)	1.62 (0.53 – 3.79)
0 – 30 Days	0.19 (0.06 – 0.44) **	0.38 (0.12 – 0.89) **	0.76 (0.25 – 1.77)
0 – 42 Days	0.14 (0.04 – 0.32) **	0.27 (0.09 – 0.63) **	0.54 (0.18 – 1.27)

* Increased and statistically significant O/E result

During the reporting interval, 16 ICSRs were retrieved using the prespecified search strategy for **myocarditis and pericarditis** (15 initial and 1 follow-up). Cumulatively, 79 ICSRs were retrieved (41 females, 38 males, age range 18-83 years when reported, median age 38.5 years). The 79 cumulative ICSRs included 80 AEs coded to the PTs pericarditis (n = 50), myocarditis (n = 22), myopericarditis (n = 6), and carditis (n = 2). Results of O/E analyses showed an increased observed rate that was statistically significant for 0-7, 0-14, and 0-30 days risk windows. When stratified by age and sex, O/E analyses revealed an increased observed rate that was statistically significant in the total male group, the 0-29-year-old male group, the total female group, and the 20-49-year-old female group.

Table 12: O/E analysis of myocarditis and pericarditis with sensitivity analysis for all cumulative AEs (PSUR pp. 112-113, Table 28).

Risk Window	O/E Rate Ratio (95% CI)	Assuming 50% Underreporting	Assuming 75% Underreporting
All AEs			
0 – 7 Days	5.20 (3.99 – 6.65) *	10.39 (7.99 – 13.30) *	20.79 (15.97 – 26.60) *
0 – 14 Days	2.93 (2.29 – 3.69) *	5.86 (4.58 – 7.39) *	11.72 (9.15 – 14.78) *
0 – 30 Days	1.58 (1.24 – 1.97) *	3.15 (2.48 – 3.95) *	6.30 (4.97 – 7.89) *
0 – 42 Days	1.20 (0.95 – 1.50)	2.41 (1.90 – 3.01) *	4.81 (3.80 – 6.01) *
Dose 1			
0 – 7 Days	2.12 (0.78 – 4.62)	4.24 (1.56 – 9.23) *	8.48 (3.11 – 18.47) *
0 – 14 Days	1.06 (0.39 – 2.31)	2.12 (0.78 – 4.61)	4.24 (1.55 – 9.23) *
0 – 30 Days	0.71 (0.26 – 1.54)	1.41 (0.52 – 3.08)	2.83 (1.04 – 6.16) *
0 – 42 Days	0.71 (0.26 – 1.54)	1.41 (0.52 – 3.08)	2.83 (1.04 – 6.16) *
Dose 2			
0 – 7 Days	2.29 (0.74 – 5.34)	4.58 (1.48 – 10.69) *	9.16 (2.97 – 21.38) *
0 – 14 Days	1.14 (0.37 – 2.67)	2.29 (0.74 – 5.34)	4.57 (1.48 – 10.68) *
0 – 30 Days	0.64 (0.24 – 1.40)	1.28 (0.47 – 2.79)	1.57 (0.94 – 5.58)
0 – 42 Days	0.46 (0.17 – 1.00)	0.92 (0.34 – 2.00)	1.83 (0.67 – 3.99)
Booster			
0 – 7 Days	0.56 (0.15 – 1.44)	1.13 (0.31 – 2.88)	2.25 (0.61 – 5.76)
0 – 14 Days	0.35 (0.11 – 0.82) **	0.70 (0.23 – 1.64)	1.41 (0.46 – 3.28)
0 – 30 Days	0.16 (0.05 – 0.38) **	0.33 (0.11 – 0.77) **	0.66 (0.21 – 1.54)
0 – 42 Days	0.12 (0.04 – 0.27) **	0.24 (0.08 – 0.55) **	0.47 (0.15 – 1.10)

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

The MAH notes that myocarditis and pericarditis has been identified as a confirmed signal and an important identified risk. It states that 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.

Paraesthesia. The signal of paraesthesia was validated on 27 May 2022 and designated as confirmed on 27 June 2022. The CCDS has been updated to include paraesthesia in section 4.8. The MAH retrieved 41 ICSRs (30 initial and 11 follow-ups) for the interval. Cumulatively, 382 ICSRs were retrieved (276 females, 105 males, 1 individual of unspecified sex, age range 13-81 years when reported) and included 476 AEs coded to the PTs paraesthesia (n = 295), hypoaesthesia (n = 127), burning sensation (n = 35), hyperaesthesia (n = 9), dysaesthesia (n = 8), and hemiparaesthesia (n = 2). The MAH states that it did not identify a safety signal.

Rapporteur assessment comment:

The MAH's analysis of rechallenge data of **menstrual disorders** (dated 18 January 2023) was assessed with the 2nd bimonthly (9th) SSR. The PRAC rapporteur agreed with the MAH that the cases of one positive and one negative rechallenge each do not really contribute to a better understanding of menstrual disorders after vaccination. The MAH's intention to continue to monitor and to re-assess the situation was endorsed. The data presented in the present PSUR correspond to those in the addendum SER, which was included in the 2nd bimonthly (9th) SSR. However, in the 2nd bimonthly (9th) SSR, the MAH reports having retrieved 113 ICSRs on MedDRA high level group term (HLGT) *menstrual cycle and uterine bleeding disorders* cumulatively through 31 December 2022 in its safety database. Using the same search strategy, the same MedDRA version 25.1, and the same time period, only 106 ICSRs were identified according to the current PSUR. The number of cases with information on rechallenge is given as two in

both reports.

Regarding the signals of diarrhoea, dyspnoea and tinnitus, the MAH was asked for supplementary information within the next SSR. With the PRAC decision in March 2023, the requirement for SSRs (last bimonthly) was discontinued. Therefore, answers to the questions in section 6 of the assessment report for the 2nd bimonthly (9th) SSR are presented in this 3rd PSUR.

Assessment report for the 2nd bimonthly (9th) SSR, PRAC rapporteur request for supplementary information

1) Signal of diarrhoea: The MAH is kindly asked to repeat its analysis using the HLT diarrhoea (excl infective).

Addendum to the SER on **diarrhoea**, dated 06 July 2023 (PSUR pp. 719-722, Appendix 21): The MAH ran a search in its safety database using the HLT diarrhoea (excl infective) and did not identify any new cases by this expanded search strategy. It concludes that diarrhoea remains a refuted signal at this time.

Comment: A causality assessment of cases without seriousness criteria is still not provided. However, the update of the Nuvaxovid surveillance plan to include the HLT diarrhoea (exl infective) is endorsed. Overall, no new aspects result from this addendum to the SER.

2) Signal of dyspnoea:

a. Only cases with seriousness criteria of hospitalisation (n = 24) or death (n = 1) were reviewed at the case level, i.e. 25 out of 96 serious cases (medically significant, n = 66; disability, n = 1; other, n = 4) of a total of 242 ICSRs. The MAH is kindly asked to justify this selection and to include at least all serious cases in its analysis.

b. The sum of the ICSRs for the respective event outcome exceeds the total number of cases (SSR p. 3596, Appendix 22, Table 7). The MAH is kindly asked to give reasons for this and to specify whether only the outcome of the events dyspnoea and dyspnoea exertional is meant here.

c. According to Table 7 (SSR p. 3596, Appendix 22), the PT pericarditis was co-reported in 12 ICSRs (5%). It is therefore surprising that the MAH's search strategy for myocarditis/pericarditis identified only five cases which co-described dyspnoea. The MAH is kindly asked to give reasons for this.

Addendum to the SER on **dyspnoea**, dated 17 July 2023 (PSUR pp. 723-746, Appendix 22): The MAH notes that its search strategy captured a total of 80 serious cases. Medically significant cases meeting only the important medical events (IME) criteria, and no additional criteria, for example cases not reporting a hospitalisation or death were previously omitted from the case series table. These cases are now tabulated. In reply to item 2b, the MAH states that event-level outcomes were summarised for all co-reported PTs and not restricted to the events under review. A table of updated event outcomes is provided. To item 2c the MAH replies that cases arising from the dyspnoea search strategy depicted in SSR 9, Appendix 22, Table 7 include serious/non-serious cases with the co-reported PT pericarditis (n = 12), but the myocarditis/pericarditis summary (SSR 9, Appendix 22, Table 8) includes a subset of the myocarditis/pericarditis cases meeting hospitalisation seriousness criteria. It states that additional cases of dyspnoea meeting other seriousness criteria have now been reviewed for completeness. Besides, the MAH expanded its original search strategy to include the following MedDRA PTs: dyspnoea, dyspnoea exertional, dyspnoea at rest, orthopnoea, laryngeal dyspnoea, and use of accessory respiratory muscles, with a DLP of 30 November 2022 (dyspnoea SER DLP 29 November 2022). However, no additional ICSRs were retrieved by the added search terms. Cases that were serious due to medically significant criterion were reviewed and included in the case series analysis. The MAH concludes that no consistent diagnostic pattern was seen for ICSRs that did not fall into categories of anaphylaxis or myocarditis/pericarditis.

Comment: The MAH's addendum to its SER on dyspnoea is acceptable.

3) Signal tinnitus:

a. The MAH is kindly asked to discuss possible pathophysiological mechanisms that may underlie tinnitus following the administration of Nuvaxovid. Preclinical data and literature should be considered.

b. The MAH is kindly asked to provide a causality analysis of all serious and non-serious cases reporting tinnitus. The World Health Organisation (WHO) causality assessment of an adverse event following immunisation (AEFI) should be applied (https://www.who.int/publications/i/item/9789241516990).

Addendum to the SER on **tinnitus**, dated 18 July 2023 (PSUR pp. 747-775, Appendix 23): The MAH points out that the exact mechanisms for the development of tinnitus in humans is not known and that is likely that a variety of triggers interact with a complex neuro-otologic system in the generation and maintenance of tinnitus. Four proposed theories for tinnitus following COVID-19 vaccination include cross-reactivity between anti-spike SARS-CoV-2 antibodies and otologic antigens also described as molecular mimicry, non-specific autoimmune/inflammatory reactions affecting the circuitry of the neuro-otologic tissue, direct ototoxicity from a component of the vaccine or as a component of symptoms associated with the limbic system activated in anxiety reactions. The MAH summarises these hypotheses to support the inclusion of tinnitus as a post-marketing adverse reaction in the CCDS. It notes that preclinical studies data following the administration of Nuvaxovid did not identify observations suggesting possible pathophysiological mechanisms that may underlie tinnitus. In reply to item 3b, the MAH states, as in its initial SER dated 13 January 2023, that a search of the safety database was performed with DLP 16 November 2022. 67 ICSRs reported the MedDRA PT tinnitus. All 15 serious and 52 non-serious cases are summarised and tabulated including a causality assessment. The MAH concludes that though no known pathophysiologic mechanism has been elucidated to explain the temporal association between COVID-19 vaccination and tinnitus, there are plausible biologic mechanisms.

Comment: Of the 15 serious cases, the MAH rates the causal association to the vaccine as consistent in four cases, indeterminate in four cases, inconsistent in five cases, and unclassifiable in two cases. The rationale in the causality assessment is not always comprehensible. Causality in cases reporting other PTs at the same time was assessed sometimes as inconsistent (e.g. [redacted], sometimes as consistent (e.g. [redacted]. The same standards should be applied for the assessment, at least within an analysis. Further, an assessment should be made at the case level, not at the PT level.

Of the 52 non-serious cases, the MAH rates the causal association to the vaccine as consistent in 17 cases, indeterminate in 11 cases, inconsistent in 6 cases, and unclassifiable in 18 cases. Here, too, the causality assessment cannot always be followed, for example in case [redacted] (it is not clear from the summary which underlying or emerging conditions were present here). In case [redacted] causality was rated as unclassifiable while in similar cases the rating consistent (e.g. case [redacted]) or indeterminate (e.g. case [redacted]) was chosen. Not all cases might have been evaluated applying the same criteria. Sufficient definitive evidence for the vaccine causing the individual event will not exist in most cases, not only in those classified as having indeterminate causality. The MAH should explain why the causality of some cases with appropriate TTO was rated as consistent, the causality of other similar cases as indeterminate.

O/E analyses were not performed for this signal.

According to the 2nd bimonthly (9th) SSR, the MAH did not observe group differences in clinical trials. Tables 3-5 (2nd bimonthly [9th] SSR pp. 3637-3638, Appendix 23) give unsolicited AE reporting rates (MedDRA PT tinnitus) between 0% and 0.1% of participants in vaccine groups and between 0% and <0.1% in placebo groups. In summary, it is still not clear on what evidence the MAH's conclusion to include tinnitus in the product information is based. Even if there are hypotheses linking a vaccination to the emergence of tinnitus, this is not a justification for labelling tinnitus. By analogy, a vast number of

other diseases without sufficient data supporting a causal association would then also have to be included in SmPC section 4.8. Besides, if, as the MAH notes, tinnitus has been reported in a pattern consistent with typically associated stress or anxiety-related vaccination reactions (2nd bimonthly [9th] SSR p. 3648), tinnitus would have to be labelled for all products within the class. Regarding vaccines against COVID-19, this is so far only the case for Vaxzevria and Jcovden. Therefore, the PRAC rapporteur suggests that tinnitus should continue to be monitored and reported on in the next PSURs. However, the topic can be discussed controversially and it's at the MAH's discretion to include tinnitus in the product information.

The MAH also provides the SER on **sensorineural hearing loss**, dated 20 July 2023 (PSUR pp. 776-809, Appendix 24): A safety signal of sensorineural hearing loss (SNHL) with Nuvaxovid was identified and validated on 15 June 2023 pursuant to a request for evaluation by the Therapeutic Goods Administration (TGA) in response to TGA's November-December 2022 disproportionality analysis report. The request specified the analysis of hearing loss cases including age-stratified and age-specific observed versus expected analyses. The MAH refers to a study which examined cases of SNHL across 5.5 million Finnish residents and found no increased risk of SNHL following vaccination with Vaxzevria, Comirnaty and Spikevax (Nieminen TA. JAMA Otolaryngol Head Neck Surg 2023;149(2):133-140. doi: 10.1001/jamaoto.2022.4154). For this SER, the MAH reviewed clinical trial data across active and placebo arms of study 2019nCoV-301 according to the MedDRA SMQ hearing and vestibular disorders (DLP of 23 November 2022). It did not identify an imbalance related to SNHL.

Table 1 Summary of Number of Events and the Events Rates for Hearing and Vestibular Disorders (SMQ) Scope: Broad

Pre-crossover Period: Number of events and event rates (Rate per 100 person years)		
MedDRA Preferred term	**SARS-CoV-2rS (5µg) + Matrix-M1 adjuvant (50 µg) (N=19,735)**	**Placebo (N=9847)**
Deafness	1 (0.01)	1 (0.03)
Post-crossover Period: Number of events and event rates (Rate per 100 person years)		
MedDRA Preferred term	**SARS-CoV-2 rS (5 µg) +Matrix-M1 adjuvant (50 µg) (N=6416)**	**Placebo (N=15298)**
Deafness neurosensory	0 (0.00)	1 (0.01)
Hypoacusis	0 (0.00)	1 (0.01)
Reported in Booster Period: Number of events and event rates (Rate per 100 person years)		
MedDRA Preferred term	**SARS-CoV-2 rS (5 µg) +Matrix-M1 adjuvant (50 µg) (N=13353)**	
Deafness neurosensory	1 (0.01)	

Further, a cumulative search of the post-authorisation safety database was performed with the MedDRA HLT auditory nerve disorder and HLT hearing loss with DLP 14 June 2023. All post authorisation ICSRs were reviewed at the case level and in aggregate for evidence of causality. According to the MAH, 19 SNHL cases (all serious) were reported with a TTO ranging from 0 to 56 days after vaccination (6 males, 13 females, age range 22-73 years when reported). Positive rechallenge of sudden hearing loss was noted in two reports. Seven reports had unilateral hearing loss, while three reports had bilateral hearing loss. The event outcome was described as not recovered/not resolved in 10 cases, as recovering/resolving in four cases, as recovered/ resolved in three cases, and as recovered with sequelae in one case. The MAH states that, of the 19 post-authorisation cases identified, 10 had confounders including evidence of concurrent infection, underlying autoimmune disease, tachycardia possibly associated with stress or anxiety, and history of traumatic deafness. The overall and age-stratified O/E ratios were significantly lower than 1.

Table 5 Age Stratified O/E Results

	Observed	Expected	O/E ratio (95% CI)
Overall	19	79.01	0.24 (0.14, 0.38)
<18 years	0	0.31	0.00 (0.00, 11.95)
18-34 years	5	7.13	0.70 (0.23, 1.64)
35-44 years	4	10.64	0.38 (0.10, 0.96)
45-54 years	1	17.37	0.06 (0.00, 0.32)
55-64 years	4	20.44	0.20 (0.05, 0.50)
65+ years	3	24.52	0.12 (0.03, 0.36)

The MAH concludes that the current evidence does not support a causal association between Nuvaxovid and SNHL.

Comment: A static reporting odds ratio evaluation in the EudraVigilance database on 13 October 2023 yielded the following results:

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

Reaction PT	ROR (-)	ROR	ROR (+)	A (N cases with P and E)	B (N cases with P and not E)	C (N cases with E and not P)	D (N cases with not P and not E)	[A+ B + C + D]
Deafness	0.69	1.66	3.99	5	2,140	16,016	11,379,393	11,397,554
Deafness unilateral	1.29	4.01	12.46	3	2,142	3,974	11,391,435	11,397,554
Hypoacusis	0.65	1.57	3.78	5	2,140	16,911	11,378,498	11,397,554
Sudden hearing loss	3.23	8.00	19.25	5	2,140	3,328	11,392,081	11,397,554
Tinnitus	3.67	4.90	6.55	47	2,098	51,829	11,343,580	11,397,554

Presumably the search in the safety database was performed with the HLT hearing losses (not hearing loss). The MAH rates the causal association to the vaccine as consistent in no case, indeterminate in two cases, inconsistent in seven cases, and unclassifiable in ten cases. In the MAH's causality assessment, it is noticeable that for example in case [redacted] the information was sufficient to assess the event tinnitus (consistent, PSUR p. 764), but not the event hypoacusis (unclassifiable, PSUR p. 796). Divergent causality assessments for co-reported tinnitus and hearing loss were also made for the cases [redacted] (indeterminate, inconsistent), [redacted] (consistent, unclassifiable), and [redacted] (indeterminate and no reported medical history, inconsistent and medical history of dizziness and recurrent sinus tachycardia), and [redacted] (indeterminate, inconsistent). Two ICSRs report a positive rechallenge: [redacted] and [redacted] In the former case, the adult patient experienced hearing loss 12 days after the first vaccination with Nuvaxovid, which lasted for one day. 26 days after the second vaccination (which was administered 21 days after the first vaccination or 9 days after the transient hearing loss), hearing loss occurred and persisted at the time of reporting (25 days after onset of the second hearing loss). In the latter case, an adult received two Nuvaxovid doses from the same batch and on the same days as the patient in the former case. Unilateral hearing loss occurred 9 days after the first vaccination and with unspecified TTO after the second vaccination.

Underreporting was not considered in the MAH's O/E analyses. In addition, the rather long 42-day risk window may contribute to diluting any potential impact of the vaccine within an actually shorter period of time. It would have been helpful to examine shorter risk intervals as well, as in the study by Baxter et al. cited by the MAH (Baxter R et al. Otolaryngol Head Neck Surg. 2016; 155[1]: 81–86. doi: 10.1177/0194599816639043; risk intervals 1-7 days, 1-14 days, 1-28 days, and 15-28 days). According to Table 2 (PSUR pp. 789-791), TTO was 0-1 days in five cases, 2-5 days in three cases, 6-10 days in three cases, 11-20 days in three cases, ≥ 21 days in four cases and unknown in two cases. Further, the limitations described by the MAH in the main part of the PSUR, such as in the calculation of age-stratified person-years, also apply to this O/E analysis ("The age-stratified person-year was calculated by applying the proportions of age distribution of all adverse reactions reported to the overall person-years

calculated").

The limitations of the analyses and the data quality of the ICSRs are noted. The MAH's argumentation can be followed, so that no further action is considered necessary at this stage with regard to this signal.

In Appendix 25 of its PSUR, the MAH summarises **updates on previously validated signals following the download of retrospective Level 2B case information from EudraVigilance**. This was triggered by a major finding during the EMA inspection in January 2023. Overall, the additional information did not change the MAH's previous assessments. However, the limited information provided in the addenda does not allow the PRAC rapporteur to make a thorough assessment here.

2.3. Evaluation of risks and safety topics under monitoring

The MAH provides information on **AESIs** for which there has been no signal so far.

Autoimmune hepatitis. No ICSR was retrieved for the interval, and one ICSR was retrieved cumulatively, concerning a 44-year-old female. This ICSR included one AE coded to the PT autoimmune hepatitis. The MAH considers the causality for the event as indeterminate, with an unlikely temporal association (TTO 92 days). As the TTO for this single AE fell outside the risk window of 0-42 days, the AE did not meet the inclusion criteria for the observed count for O/E analyses. The MAH did not identify a safety signal.

Autoimmune thyroiditis. No ICSR was retrieved for the interval, and three ICSRs were retrieved cumulatively. These ICSRs concerned females and included three AEs coded to the PTs thyroiditis (n = 1), autoimmune thyroiditis (n = 1), and Graves' disease (n = 1). The MAH notes that O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate. No safety signal was identified.

Bell's palsy. 13 initial ICSRs were retrieved for the interval, and 23 ICSRs were retrieved cumulatively (13 females, 10 males, age range 20-77 years when reported, median age 47 years). The 23 cumulative ICSRs included 24 AEs coded to the PTs facial paralysis (n = 20), Bell's palsy (n = 3) and facial paresis (n = 1). The MAH notes that all ICSRs met TTO inclusion criteria and results of O/E and sensitivity analyses showed lower than expected rates, and did not identify a safety signal.

Cerebral venous sinus thrombosis. One ICSR was retrieved for the interval and cumulatively (male, 67 years), including one AE coded to the PT cerebral venous sinus thrombosis. The single ICSR met TTO inclusion criteria and O/E analysis showed the observed count was increased compared to expected count at 50% and 75% sensitivity, but this increase was not statistically significant. No safety signal was identified.

Chronic fatigue syndrome. No ICSR was retrieved for the interval, and two ICSRs were retrieved cumulatively (1 female and 1 male, ages 44 and 32 years, respectively). These two ICSRs included two AEs coded to the PT chronic fatigue syndrome. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate. No safety signal was identified.

Encephalitis and encephalomyelitis. No ICSR was retrieved for the interval, and three ICSRs were retrieved cumulatively (2 females, 1 male; age range 42-67 years, median age 57 years). These ICSRs included three AEs coded to the PTs noninfective encephalitis (n = 2) and encephalitis (n = 1). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate. No safety signal was identified.

Fibromyalgia. One initial ICSR was retrieved for the interval, and two ICSRs were retrieved cumulatively (1 female age 49 years, 1 male of unknown age). These ICSRs included two AEs coded to the PT

fibromyalgia, though in one ICSR it was reported verbatim "fibromyalgia worsened". O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate. No safety signal was identified.

Generalised convulsions. Four (three initial and one follow-up) ICSRs were retrieved for the interval, and 13 ICSRs cumulatively (10 females, 3 males, age range 17-76 years, median age 30 years). These 13 ICSRs included 14 AEs coded to the 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). Eleven AEs met inclusion criteria for O/E analyses for the 0-7-day risk window. O/E analysis showed that the overall observed rate was lower than the expected rate for risk windows 0-1, 0-2 and 0-7 days. The analysis calculated using risk window of 0-1 days showed the observed count was increased compared to expected count at 50% and 75% sensitivity, but this increase was not statistically significant. The MAH did not identify a safety signal.

Guillain-Barré syndrome. Four initial ICSRs were retrieved for the interval, and 7 ICSRs cumulatively. These 7 ICSRs included 7 AEs coded to the PT Guillain-Barré syndrome (n = 7). Five of 7 ICSRs met TTO inclusion criteria for O/E analyses, which showed the observed rate was increased compared to expected rate at 50% and 75% underreporting, but this increase was not statistically significant. No safety signal was identified.

Haemorrhagic stroke. Three initial ICSRs were retrieved for the interval, and 10 ICSRs were retrieved cumulatively (4 females, 6 males, age range 20096 years, median age 60 years). These 10 cumulative ICSRs included 10 AEs coded to the PT cerebrovascular accident (n = 10). Because the type of cerebrovascular accident was not indicated, the same 10 ICSRs also were retrieved by the search strategy for ischaemic stroke. Six ICSRs met TTO inclusion criteria and results of O/E analyses showed a lower than expected rate. No safety signal was identified.

Ischaemic stroke. Five initial ICSRs were retrieved for the interval, and 15 ICSRs were retrieved cumulatively (7 females, 8 males, age range 20-96 years, median age 60 years). These 15 ICSRs included 15 AEs coded to the PTs cerebrovascular accident (n = 10), brain stem infarction (n = 1), carotid artery disease (n = 1), ischaemic stroke (n = 1), transient ischaemic attack (n = 1) and cerebral infarction (n = 1). 11 ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. No safety signal was identified.

Multiple sclerosis. No ICSR was retrieved for the interval, and three ICSRs were retrieved cumulatively (two females and one male, age range 36-63 years, median age 41 years). The three cumulative ICSRs included three AEs coded to the PTs multiple sclerosis relapse (n = 2) and multiple sclerosis (n = 1). All ICSRs met the TTO inclusion criteria and results of O/E analyses showed a lower than the expected rate. No safety signal was identified.

Multisystem inflammatory syndrome in children. One initial ICSR was retrieved for the interval. Cumulatively, no cases were retrieved involving children and one ICSR was retrieved for a female adult (82 years old, including one AE coded to the PT multisystem inflammatory syndrome). The single ICSR met TTO inclusion criteria and results of O/E and sensitivity analyses showed lower than expected rates. No safety signal was identified.

Myasthenia gravis. One initial ICSR was retrieved for the interval, and one ICSR was retrieved cumulatively (male, 69 years old). This ICSR included one AE coded to the PT myasthenia gravis and met TTO inclusion criteria for O/E analysis. Results of O/E sensitivity analyses showed lower than expected rates. No safety signal was identified.

Myocardial infarction. Two initial ICSRs were retrieved for the interval, and 13 ICSRs cumulatively (5 females, 8 males, age range 24-93 years when reported, median age 50 years). The 13 cumulative ICSRs

included 13 AEs coded to the PTs troponin increased (n = 6), acute myocardial infarction (n = 3), myocardial infarction (n = 3), and acute coronary syndrome (n = 1). Ten AEs met TTO inclusion criteria and results of O/E analyses showed lower than expected rate. No safety signal was identified.

Optic neuritis. No ICSR was retrieved for the interval, and one ICSR was retrieved cumulatively. This single ICSR concerned a 37-year-old female, included one AE coded to the PT optic neuritis and met the TTO inclusion criteria. Results of O/E analyses showed lower than expected rates. No safety signal was identified.

Postural orthostatic tachycardia syndrome. No ICSR was retrieved for the interval. Two ICSRs were retrieved cumulatively (one male, one female, ages 32 and 38 years, respectively) and included two AEs coded to the PT postural orthostatic tachycardia syndrome. Results of O/E analyses showed lower than expected rates. The MAH notes that that background rates for postural orthostatic tachycardia syndrome were captured from a study done in Finland (Skufca J et al. Papillomavirus Res 2017;3:91-96, doi: 10.1016/j.pvr.2017.03.001), and that the rarity of the diagnosis leads to difficulty in finding a reliable background rate. It states that its analysis did not suggest a safety signal.

Pre-eclampsia. One follow-up ICSR was retrieved for the interval. Cumulatively, one ICSR was retrieved, concerned a 38-year-old female and included one AE coded to the PT pre-eclampsia. O/E analysis was not performed due to inability to accurately determine exposure in pregnant females alone and indeterminate risk windows. The MAH did not identify a safety signal.

Rheumatoid arthritis. Three initial ICSRs were retrieved for the interval. Six ICSRs were retrieved cumulatively (3 females, 3 males, age range 29-74 years when reported, median age 49 years) and included six AEs coded to the PTs rheumatoid arthritis (n = 4), polyarthritis (n = 1) and rheumatoid lung (n = 1). Three ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. No safety signal was identified.

Spontaneous abortion. No ICSR was retrieved for the interval. Four ICSRs were retrieved cumulatively (4 females, age range 23-31 years when reported) and included four AEs coded to the PT abortion spontaneous. No O/E analysis could be performed as the exposure is unknown in women of childbearing age. No safety signal was identified.

Thrombocytopenia. Two initial ICSRs were retrieved for the interval. Cumulatively, 7 ICSRs were retrieved (6 females, 1 male, age range 23-69 years, median age 36 years) and included 8 AEs coded to the PTs thrombocytopenia (n = 5), immune thrombocytopenia (n = 2) and thrombosis with thrombocytopenia syndrome (n = 1). All ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. No safety signal was identified.

Thrombosis with thrombocytopenia syndrome. One initial ICSR was retrieved for the interval. Cumulatively, one ICSR was retrieved (male, 69 years), included one AE coded to the PT thrombosis with thrombocytopenia syndrome and met TTO inclusion criteria. Results of O/E analyses showed lower than expected rates. No safety signal was identified.

Vaccine associated enhanced disease (important potential risk). Six initial ICSRs were retrieved for the interval. Cumulatively, six ICSRs were retrieved (6 males, age range 33-71 years, median age 55 years) and included six AEs coded to the PT antibody-dependent enhancement. The MAH states that O/E analyses was not performed as it is not possible to determine expected rate for this AE, given that vaccine exposure is necessary to develop the condition. It did not identify a safety signal.

Venous thromboembolism. Six ICSRs were retrieved for the interval (4 initial and 2 follow-up). Cumulatively, 22 ICSRs were retrieved (13 females, 9 males, age range 29-85 years when reported, median age 50 years) and included 25 AEs coded to the PTs pulmonary embolism (n = 12), thrombophlebitis (n = 4), deep vein thrombosis (n = 3), venous thrombosis (n = 3), superficial vein

thrombosis (n = 2), and cerebral venous sinus thrombosis (n = 1). 18 AEs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. No safety signal was identified.

Besides, the MAH queried its global vaccine safety database for **additional safety topics**.

Death, all cause. 19 initial ICSRs (thereof 16 from South Korea) were retrieved for the interval. Cumulatively, 28 ICSRs were retrieved (13 females, 15 males, age range 13-96 years when reported, median age 74.5 years) and included 49 fatal AEs. The most frequently reported PTs (n > 1) with fatal outcome were death (n = 11), dyspnoea (n = 4), pyrexia (n = 3), headache (n = 2), dizziness (n = 2), adverse event following immunization (n = 2), and cerebrovascular accident (n = 2). 26 of the 28 cumulative ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. The MAH did not identify a safety signal.

Cholecystitis. No ICSR was retrieved during the interval, and cumulatively, 8 ICSRs were retrieved (5 females, 3 males, age range 38-84 years when reported, median age 44 years). These 8 ICSRs included 8 AEs coded to the PTs abnormal faeces (n = 3), jaundice (n = 2), blood bilirubin increased (n = 1), faeces pale (n = 1) and gallbladder disorder (n = 1). The MAH states that no change in the characteristics of this event has been identified following cumulative review.

Diarrhoea. 45 ICSRs were retrieved for the interval (40 initial and 5 follow-ups), thereof 30 from South Korea. Cumulatively, 132 ICSRs were retrieved (107 females, 25 males, age range 18-86 years when reported, median age 43.5 years) and included 133 AEs coded to the PT diarrhoea. According to the MAH, no safety signal was identified.

Herpes zoster. Four initial ICSRs were retrieved during the reporting interval. Cumulatively, 40 ICSRs were retrieved (11 males, 28 females, 1 individual of unspecified sex, age range 24-76 years when reported, median age 53 years) and included 42 AEs coded to the 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). O/E and sensitivity analyses results showed that the observed count was lower than the expected count for all risk windows (0-7 days, 0-14 days, 0-30 days and 0-42 days). No safety signal was identified.

Inflammatory eye disorders. 7 ICSRs were retrieved for the interval (4 initial and 3 follow-ups). Cumulatively, 61 ICSRs were retrieved (49 females, 12 males, age range 16-72 years when reported, median age 46 years) and included 69 AEs coded to the PTs eye swelling (n = 17), photophobia (n = 9), ocular hyperaemia (n = 8), diplopia (n = 6), swelling of eyelid (n = 5), eye inflammation (n = 5), lacrimation increased (n = 5), eye irritation (n = 4), eye pruritus (n = 3), eye discharge (n = 2), eyelid oedema (n =2), idiopathic orbital inflammation (n = 1), iridocyclitis (n = 1), and uveitis (n = 1). The MAH did not identify a safety signal.

Menstrual disorders. Following the validation of the signal on 27 June 2022, the signal has been refuted on 27 June 2022 and the topic is being monitored via routine pharmacovigilance activities. 32 ICSRs were retrieved for the interval (26 initial and 6 follow-ups). Cumulatively, 130 ICSRs were retrieved (130 females, age range 20-73 years when reported) and included 198 AEs. The most frequently reported AEs (n > 10) were coded to the PTs menstrual disorder (n = 49), heavy menstrual bleeding (n = 39), dysmenorrhoea (n = 18), abnormal uterine bleeding (n = 18), menstruation irregular (n = 17), amenorrhoea (n = 15), polymenorrhoea (n = 12), and intermenstrual bleeding (n = 11). No safety signal was identified. The MAH notes that there were no new positive rechallenge cases during this reporting interval.

Reactogenicity profile – second dose and boosters (based on impurity levels). 28 ICSRs were retrieved for the interval (23 initial and 5 follow-ups). Cumulatively, 130 ICSRs were retrieved for second dose and boosters, 128 of which contained batch numbers (39 males, 91 females, age range 17-93 years

when reported). These 130 ICSRs included 925 AEs. The most frequently reported AEs (n > 20) were coded to the PTs headache (n = 57), fatigue (n = 54), pyrexia (n = 37), malaise (n = 34), injection site pain (n = 30), chills (n = 27), nausea (n = 25), arthralgia (n = 25), myalgia (n = 23), and pain in extremity (n = 21). The MAH did not identify any trends related to reactogenicity based on impurity levels specifically after a second dose and/or a booster.

Review of safety concerns in elderly. 384 ICSRs were retrieved for the interval (378 initial and 6 follow-ups), thereof 298 from South Korea. Cumulatively, 650 ICSRs were retrieved (422 females, 221 males, 7 individuals of unknown sex, age range 65-96 years when reported) and included 1,846 AEs. The most frequently reported AEs (n > 30) were coded to the PTs myalgia (n = 121), headache (n = 105), dizziness (n = 81), hypersensitivity (n = 80), injection site pain (n = 54), pyrexia (n = 54), nausea (n = 51), fatigue (n = 49), dyspnoea (n = 42), chills (n = 37), rash (n = 37), pruritus (n = 36), chest pain (n = 35), arthralgia (n = 35), urticaria (n = 32), and COVID-19 immunisation (n = 31). The MAH states that no safety signal was identified.

Off-label paediatric use (less than 12 years). 7 initial ICSRs were retrieved for the interval. Cumulatively, 11 ICSRs were retrieved (4 females, 1 male, 6 individuals of unspecified sex, age range from 4-9 years for 8 ICSRs when reported, 2 neonates and 1 infant of unspecified age) and contained 18 non-serious AEs. The MAH's review of the reports did not reveal a safety signal.

Vaccine anxiety-related reactions. Five ICSRs were retrieved for the interval (4 initial and 1 follow-up). Cumulatively, 52 ICSRs were retrieved (43 females, 7 males, 2 individuals of unspecified sex, age range 19-65 years when reported) and included 52 AEs coded to the PTs anxiety (n = 40), nervousness (n = 6), agitation (n = 4), stress (n = 1), and tension (n = 1). The MAH did not identify a safety signal.

Vaccination failures/lack of efficacy. By definition, a case of vaccination failure applies when (i) associated COVID-19 symptoms are reported, (ii) events occur 7 or more days past the date of the second or booster administration, and (iii) a positive diagnostic test for COVID-19 is reported. Seven ICSRs were retrieved for the interval (4 initial and 3 follow-ups). Cumulatively, 12 ICSRs were retrieved (9 females, 3 males, age range 20-74 years when reported) and included 12 AEs coded to the PTs vaccination failure (n = 11) and paradoxical drug reaction (n = 1). The MAH did not identify a safety signal.

Rapporteur assessment comment:

In comparison to the proportion of doses applied during the reporting interval to all doses applied cumulatively, quite a large number of AESIs were reported in the 6-month interval covered by this PSUR. The MAH attributes the relatively high number of AEs to the fact that during the reporting interval many reports from South Korea were included in the database.

The sentence "As the broad search strategy is less specific, all reports retrieved by both the narrow and broad search strategies were adjudicated against the Brighton Collaboration (BC) case definitions for myocarditis and pericarditis." (PSUR p. 135) could be misunderstood, since all reports retrieved by the narrow search strategy are also included in the list retrieved by the broad search strategy. In its response to the request for supplementary information, the MAH confirmed that all reports retrieved by the broad search strategy were adjudicated and classified according to BC case definitions.

During the reporting interval, six initial ICSRs from South Korea were retrieved for vaccine associated enhanced disease and coded to the MedDRA PT 10088388. However, no events of COVID-19 were identified with the limited information provided.

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

2.4. Characterisation of risks

The MAH refers to the latest version of the EU RMP approved on 06 February 2023, part II, module SVII. There are no additional risk minimisation measures in place for Nuvaxovid.

New information on important identified risks – myocarditis and/or pericarditis. The MAH queried its global vaccine safety database using the broad search strategy – standardised MedDRA query (SMQ) (broad) noninfectious myocarditis/pericarditis, including the HLTs infectious myocarditis, infectious pericarditis, noninfectious myocarditis, and noninfectious pericarditis. The MAH states that all reports retrieved by both the narrow and broad search strategies were adjudicated against the BC case definitions for myocarditis and pericarditis. 25 ICSRs (21 initial and 4 follow-ups) were retrieved during the reporting interval. Cumulatively, the broad search strategy yielded 120 ICSRs (66 females, 54 males). Recurrent myocarditis/pericarditis was noted in 18 cases. Four reports met BC case definition level 1, 30 level 2, 9 level 3, and 4 level 1-3 (exact level unknown). TTO was 0-7 days in the majority of cases (n = 69, 57.5%). The MAH concludes that no significant safety information was received on this important identified risk during the reporting interval that would alter its already established characterisation.

New information on other identified risks not categorised as important. During the reporting interval and cumulatively, anaphylaxis and tinnitus were identified risks for Nuvaxovid that were not categorised as important.

New information on important potential risks – vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease. See section 2.3.

New information on other potential risks not categorised as important. Not applicable.

Update on missing information.

- **Use in pregnancy.** Six ICSRs were retrieved for the interval (5 initial and 1 follow-up). Cumulatively, 12 ICSRs were retrieved (12 females, age range 21-57 years). **Use while breastfeeding.** One initial ICSR was retrieved for the interval. Cumulatively, 3 ICSRs were retrieved (3 females, ages 29, 30 and 38 years, respectively). The MAH notes that none of the reports of use during pregnancy and breastfeeding raised any safety concerns.
- **Use in immunocompromised patients.** One initial ICSR was retrieved for the interval. Cumulatively, five ICSRs were retrieved (4 females and 1 male, age range 44-93 years) and included 19 AEs. The MAH states that its 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).** 137 ICSRs were retrieved for the interval (119 initial and 18 follow-ups). Cumulatively, 519 ICSRs were retrieved (370 females, 138 males, 11 individuals of unspecified sex, age range 16-96 years when reported) and included 2,317 AEs (thereof 581 serious AEs and 20 AEs with a fatal outcome). The most frequently reported PTs (n > 30) were headache (n = 103), fatigue (n = 100), pyrexia (n = 60), myalgia (n = 55), chest pain (n = 49), dizziness (n = 48), nausea (n = 43), pain in extremity (n = 41), arthralgia (n = 40), malaise (n = 38), chills (n = 37), pain (n = 33), dyspnoea (n = 32), paraesthesia (n = 32), palpitations (n = 32) and COVID-19 immunisation (n = 32). The MAH concludes that its 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.

- **Use in patients with autoimmune or inflammatory disorders.** 35 ICSRs were retrieved for the interval (29 initial and 6 follow-ups). Cumulatively, 163 ICSRs were retrieved (137 females, 26 males, age range 21-94 years when reported) and included 789 AEs (thereof 209 serious AEs and 18 fatal AEs). The most frequently reported PTs (n >20) were headache (n = 39), fatigue (n = 29) and pyrexia (n = 26). The MAH notes that its 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.
- **Interaction with other vaccines.** No ICSR was retrieved for the interval. Cumulatively, one ICSR was retrieved, but did not meet the inclusion criteria after assessment.
- **Long-term safety.** During the reporting interval and cumulatively, the MAH did not identify any new information determining long-term safety.

Rapporteur assessment comment:

The safety concerns remain unchanged.

3. Benefit evaluation

The MAH refers to information on efficacy at the beginning of the reporting interval from the CCDS version 6.0 (effective 10 August 2022) and summarises two placebo-controlled phase 3 studies, 2019nCoV-301 conducted in North America and 2019nCoV-302 conducted in the UK. Among participants 18 years of age and older in the 2019nCoV-301 study, vaccine efficacy to prevent the onset of COVID-19 from seven days after dose 2 was 90.4% (95% CI: 82.9-94.6). In study 2019nCoV-302, vaccine efficacy was 89.7% (95% CI: 80.2-94.6) and consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years). In addition, results on immunogenicity are cited from studies 2019nCoV-301, 2019nCoV-307 and COV-BOOST.

Rapporteur assessment comment:

In the final analysis of the 2019nCoV-302 study (27 July 2021, 6 months after first vaccination of the last participant, PSUR section 7.1.1), vaccine efficacy was reported to be slightly lower (82.6%, 95% CI: 72.9-88.8) than the "baseline efficacy" at the beginning of the reporting interval (analysis of 29 January 2021, median surveillance time 56 days, PSUR sections 7.1.1 and 17.1.2; vaccine efficacy 89.7%, 95% CI: 80.2-94.6).

The new data presented on efficacy does not alter previous assessments.

Note: The subsection on prevention of COVID-19 in PSUR section 18.1 is not up-to-date. During the PSUR reporting interval and prior to DLP 19 June 2023, another vaccine was authorised (Bimervax).

4. Benefit-risk balance

The data presented does not include significant new information that alters previous assessments of efficacy or safety. The PRAC rapporteur therefore concludes that the benefit-risk ratio for Nuvaxovid in the approved indications remains positive. The MAH's commitment to continue monitoring safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines is endorsed.

5. Rapporteur Request for supplementary information

1) Although substantially fewer doses were administered during this reporting interval, there were comparatively more ICSRs. Of 2,485 spontaneously reported SAEs, 795 (32%) were reported during the reporting interval, and 4,169 (30%) of 14,091 non-serious AEs. This proportion is high as only 11% of all doses (335,128 out of 2,986,711) were administered during the reporting interval. The MAH is kindly asked to comment on the disproportionately high number of AEs in the reporting interval. In addition, it should explain why the text reports a cumulative total of 16,710 AEs (PSUR p. 42) and Appendix 5 a cumulative total of 16,576 AEs (PSUR p. 335). Also, among the SAEs reported post-marketing, at least one seems to be missing in Appendix 5.

2) The sentence "As the broad search strategy is less specific, all reports retrieved by both the narrow and broad search strategies were adjudicated against the Brighton Collaboration (BC) case definitions for myocarditis and pericarditis." (PSUR p. 135) could be misunderstood, since all reports retrieved by the narrow search strategy are also included in the list retrieved by the broad search strategy. The MAH is kindly asked to clarify whether only the cases of the narrow search strategy were classified according to BC case definitions.

3) During the reporting interval, six initial ICSRs were retrieved for vaccine associated enhanced disease and coded to the MedDRA PT 10088388. The MAH is kindly asked to present these cases in more detail.

4) In PSUR section 4.1 (p. 28), the MAH indicates that it submitted a tinnitus labelling update to EMA. However, this submission could not be traced in the EMA databases at the time of the assessment of this PSUR. The MAH is therefore requested to comment on the status of this safety variation.

6. MAH responses to Request for supplementary information

1) *Although substantially fewer doses were administered during this reporting interval, there were comparatively more ICSRs. Of 2,485 spontaneously reported SAEs, 795 (32%) were reported during the reporting interval, and 4,169 (30%) of 14,091 non-serious AEs. This proportion is high as only 11% of all doses (335,128 out of 2,986,711) were administered during the reporting interval. The MAH is kindly asked to comment on the disproportionately high number of AEs in the reporting interval.*
   In addition, it should explain why the text reports a cumulative total of 16,710 AEs (PSUR p. 42) and Appendix 5 a cumulative total of 16,576 AEs (PSUR p. 335).
   Also, among the SAEs reported post-marketing, at least one seems to be missing in Appendix 5.

MAH response:

As discussed in Section 6.3, Cumulative and Interval Summary Tabulations from Post-Authorisation Data, Page 42, NVX received two batches of 6-month legacy adverse event (AE) data (n=1,111 ICSRs out of 1,679 ICRSs received during the interval) from the Korea Institute of Drug Safety and Risk Management (KIDS) during the reporting interval. This bolus led to an apparent disproportionality that, upon review, did not generate any new signals. Going forward, Novavax will include corresponding number of ICSRs received and place any subsequent disproportionate reporting into context.

Section 6.3 (p. 42) reports the cumulative total of all AEs (n=16,710), while Appendix 5 (n=16,576) presents cumulative/interval serious and non-serious adverse reactions (AR) from post-marketing data sources, in accordance with GVP Module VII. B.5.20 Appendices to the PSUR. The difference of 134 AEs, includes two spontaneous AEs reported as not related (from [redacted] which was a case received by a business partner), and 132 AEs from non-interventional post-marketing studies and from

other solicited sources (5 of those AEs were serious related and included in a different column in Appendix 5)

The SAE noted as seemingly missing from Appendix 5 ([redacted] is a report from a non-interventional study with a serious unlisted event of pre-eclampsia assessed as not related by both the reporter and sponsor. This event was excluded from the summary tabulation of serious ARs in Appendix 5 and was included in the cumulative total of SAE in the text on page 42. Novavax commits to presenting the AEs with more clarity in the 4th PSUR.

Rapporteur assessment comment:
The MAH attributes the high number of ICSRs in the reporting interval to the delayed reports from Korea. The slightly divergent numbers of adverse events and adverse reactions in different sections of the PSUR are clarified. Issue considered resolved.

2) *The sentence "As the broad search strategy is less specific, all reports retrieved by both the narrow and broad search strategies were adjudicated against the Brighton Collaboration (BC) case definitions for myocarditis and pericarditis." (PSUR p. 135) could be misunderstood, since all reports retrieved by the narrow search strategy are also included in the list retrieved by the broad search strategy. The MAH is kindly asked to clarify whether only the cases of the narrow search strategy were classified according to BC case definitions.*

MAH response:

Novavax agrees that this language may be confusing and confirms that all reports retrieved by the broad search strategy were adjudicated and classified according to BC case definitions. Going forward, only the broad search strategies will be referenced where applicable.

Rapporteur assessment comment:
The MAH clarifies its approach, which is endorsed. Issue considered resolved.

3) *During the reporting interval, six initial ICSRs were retrieved for vaccine associated enhanced disease and coded to the MedDRA PT 10088388. The MAH is kindly asked to present these cases in more detail.*

Summary of MAH response:

The MAH summarises the six initial ICSRs reported as vaccine associated enhanced disease during the reporting interval. All reports arise from South Korea and no events of COVID-19 were identified with limited information provided.

Rapporteur assessment comment:
The 6 cases, involving 6 males aged between 33 and 71 years (median, 55 years), are presented in a table with the columns *case number*, *PT/verbatim/seriousness criteria*, *TTO*, *diagnostic evidence (BC level)*, *sponsor causality/rationale*, and *brief summary*. TTO ranged from 0 days to 3 months plus 11 days (median, 1.5 days); in 5/6 cases, TTO was between 0 and 3 days. Diagnostic tests and treatment were not reported in any case. In 3/6 cases, other conditions were described in addition to vaccine associated enhanced disease. These were dizziness, chills, nausea, and vomiting. Based on the information provided, no pattern or concern can be identified. Issue considered resolved.

4) *In PSUR section 4.1 (p. 28), the MAH indicates that it submitted a tinnitus labelling update to EMA. However, this submission could not be traced in the EMA databases at the time of the assessment of this PSUR. The MAH is therefore requested to comment on the status of this safety variation.*

MAH response:

Novavax submitted variation, tinnitus labelling update for Nuvaxovid, within grouped variations EMEA/H/C/005808/II/0045/G to implement tinnitus as a new safety signal in Nuvaxovid product information on 24 February 2023. However, considering received Updated PRAC Assessment report PSUR No.02 on 22 June 2023 with conclusion of open evaluation of tinnitus data that stated: *"The assessment of the signal evaluation reports on diarrhoea, dyspnoea, and tinnitus was taken from the review of the 9th SSR. The current PBRER does not provide any new information here. The MAH's responses to the PRAC request for supplementary information are still pending. Until then, the signals of diarrhoea, dyspnoea and tinnitus will not be closed."* Novavax decided to withdraw the variation application on 03 July 2023 and wait for evaluation of more gained data by PRAC within the PSUR No.03.

Rapporteur assessment comment:

The PRAC rapporteur is of the opinion that there is currently insufficient evidence to suggest a causal relationship between the administration of Nuvaxovid and tinnitus. It is recommended that tinnitus should continue to be monitored and reported on in the next PSURs. If the MAH deems it appropriate, it may include tinnitus in the product information. Issue considered resolved.

7. Comments from Member States

Supportive comments were received from a Member State.

PERIODIC BENEFIT-RISK EVALUATION REPORT

FOR

PRODUCT: NVX-CoV2373™ DISPERSION FOR INJECTION COVID-19 VACCINE (RECOMBINANT, ADJUVANTED) (SARS-CoV-2 rS)

ATC CODE: [J07BX03]

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Product	Marketing authorisation number(s)	Date of authorisation	Marketing Authorisation Holder
NUVAXOVID™	EMEAA/H/C/005808	20-Dec-2021	Novavax CZ a.s

AUTHORISATION PROCEDURE in the EU: Conditional Marketing Authorisation

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

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

INTERVAL COVERED BY THIS REPORT: 20-Dec-2022 to 19-Jun-2023

Date of Report: 14-Aug-2023

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:	Julia Appelskog, PhD EU QPPV Global Vaccine Safety	[redacted]
APPROVED BY:	[redacted]	
APPROVED BY:	[redacted]	

EXECUTIVE SUMMARY

Introduction

This is the third Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™ (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) recombinant (r), Spike Protein (S), adjuvanted; also referred to as NVX-CoV2373, interchangeably in the document) compiled for health authorities summarising the interval and cumulative safety data received by Novavax (NVX) for the interval 20-Dec-2022 to 19-Jun-2023. This PBRER follows: the International Conference on Harmonisation (ICH) E2C Harmonized Tripartite Guideline Periodic Benefit-Risk Evaluation Report (PBRER); European Medicines Agency (EMA) E2C guideline on PBRER; the EMA Module VII Guideline on Good Pharmacovigilance Practices (GVP) – Periodic safety update report; and EMA Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases. The periodicity of this PBRER is based on the European Union (EU) harmonised birth date (international birth date) which is 20-Dec-2021.

Medicinal Product

Nuvaxovid is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. Nuvaxovid is authorised as a two-dose primary series and as a booster in individuals 12 years and older (authorised as Covovax™ for individuals 7 years and older in India). Nuvaxovid is a purified full-length SARS-CoV-2 rS protein that is stabilised in its pre-fusion conformation. The addition of the saponin-based Matrix-M™ adjuvant facilitates- activation of the innate immune system which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies which may contribute to protection against COVID-19. The prototype SARS-CoV-2 rS nanoparticle vaccine (NVX-CoV2373) developed by NVX, constructed from the full length wild-type SARS-CoV-2 S glycoprotein based on the original Wuhan-Hu-1 strain, is administered with the saponin-based adjuvant Matrix-M for enhanced immunogenicity.

Nuvaxovid is a dispersion for intramuscular injection. One dose (0.5 milliliters [mL]) of Nuvaxovid contains 5 micrograms (µg) of the recombinant SARS-CoV-2 S protein (produced by recombinant deoxyribonucleic acid [DNA] technology using a Baculovirus expression system in an insect cell line derived from Sf9 cells of the *Spodoptera frugiperda* species), plus 50 µg of the Matrix-M adjuvant which contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of *Quillaja saponaria* Molina extract. Nuvaxovid is supplied either as a multi-dose vial of 10 doses or 5 doses (of 0.5 mL each). The dispersion is colourless to slightly yellow, clear to mildly opalescent with a pH of 7.2.

The primary series of Nuvaxovid is two doses (0.5 mL each) given 3 weeks apart. A booster dose of Nuvaxovid (0.5 mL) may be administered approximately 6 months after completion of

the primary series in adults 18 years of age and older and at least 5 months after completion of the primary series in adolescents 12 through 17 years of age. Further details on the mechanism of action, indications, pharmaceutical form(s), and instructions for use are presented in the Company Core Data Sheet (CCDS).

Worldwide Marketing Authorisation Status

SARS-CoV-2 rS with Matrix-M adjuvant is currently authorised as Nuvaxovid and Covovax in multiple countries, in the EU region and by the World Health Organisation (WHO) an agency of the United Nations, for active immunisation to prevent COVID-19 caused by SARS-CoV-2. Nuvaxovid is authorised as a primary series and as a booster vaccine for individuals over 12 years of age. In India, Covovax is additionally authorised as a primary series vaccine for individuals 7 years and older.

Changes to Reference Safety Information

The Nuvaxovid Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the CCDS Version (V) 6.0, effective date 10-Aug-2022.

During the reporting interval, the CCDS was updated to V 7.0 (effective date 02-Feb-2023) with the following safety-related changes:

- Adverse reactions from post-marketing experience under Section 4.8 'Undesirable effects' has been updated with Preferred Term (PT) "Tinnitus" in the System Organ Class (SOC) of "Ear and labyrinth disorders".
- Section 4.8 and 5.1 were updated with new safety and efficacy information in support of adolescent booster dosing.

CCDS V 7.0 was in effect at the end of the reporting interval and was used to assess expectedness of reported adverse events.

Summary of Clinical Trials

During the reporting interval, 6 clinical trials of SARS-CoV-2 rS were ongoing (2019nCoV-101 Part 2, 2019nCoV-301, 2019nCoV-311, 2019nCoV-312, 2019nCoV-503, 2019nCoV-505) and 3 clinical trials were completed (2019nCoV-302, 2019nCoV-307 and 2019nCoV-501).

Clinical Trial Exposure

Cumulatively, 59,691 participants have been exposed to either SARS-CoV-2 rS, placebo or blinded treatment in the clinical development program sponsored by NVX. Out of the 59,691 participants, 47,395 participants were exposed to SARS-CoV-2 rS, 8,460 participants were exposed to placebo and 3,836 participants were exposed to blinded treatment (2,265 participants in the 2019nCoV-503 study received either SARS-CoV-2 rS or placebo and 1,571 participants in

the 2019nCoV-CIC-E-201 study received either SARS-CoV-2 rS or COVID-19 and Influenza Combination (CIC) vaccine or quadrivalent hemagglutinin nanoparticle influenza vaccine (qNIV) or licensed influenza vaccines (Fluzone™ high dose or FLUAD™)).

Post-Authorisation Exposure

During the reporting interval, 314,830 NVX-CoV2373 doses were administered across Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, United Kingdom and the United States of America (USA) and 14,414 Covovax doses were administered in India. A total of 9,790,300 NVX-CoV2373 doses (9,784,700 NVX-CoV2373 and 5,600 Covovax doses) were distributed globally.

Cumulatively, 2,872,381 NVX-CoV2373 doses were administered in Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, United Kingdom and the USA and 41,762 Covovax doses were administered in India. A total of 112,787,170 NVX-CoV2373 doses (103,452,920 NVX-CoV2373 and 9,334,250 Covovax doses) have been distributed globally.

Overview of Interval and Cumulative Adverse Event Data from Post-authorisation experience

A total 1,679 spontaneous individual case safety reports (ICSRs) were received during the 6-month reporting interval (of which 92 ICSRs contained follow-ups), with 5,089 adverse events (AEs) (601 serious unlisted AEs, 199 serious listed AEs, 1,517 non-serious unlisted AEs, and 2,772 non-serious listed AEs). A total of 19 fatal ICSRs were reported during the 6-month interval.

Cumulatively, 4,619 spontaneous ICSRs have been received (of which 808 were follow-ups), reporting 16,710 AEs (1,790 serious unlisted AEs, 701 serious listed AEs, 6,976 non-serious unlisted AEs, and 7,243 non-serious listed AEs). A total of 28 fatal ICSRs have been reported cumulatively.

Overview of Signals: New, Ongoing, or Closed

A signal of sensorineural hearing loss was validated during the reporting interval following a 15-Jun-2023 request for assessment by the Australian Therapeutic Goods Administration. The signal evaluation was completed (refuted) on 30-Jul-2023.

Additional information related to previously validated signals of menstrual disorders, diarrhoea, dyspnoea and tinnitus were reviewed in response to observations or requests arising from the Pharmacovigilance Risk Assessment Committee (PRAC) review of the first bi-monthly summary safety report (SSR) with reviews completed shortly after the data lock of this 3rd PBRER. In addition, new information related to all validated and non-validated signals underwent review following retrospective L2B downloads.

Positive rechallenge information related to the previously validated signal of menstrual disorders was reviewed and the signal of menstrual disorders remains refuted. The signal has been closed and will continue to be monitored under routine surveillance practice. An addendum to the original review was submitted with the second bi-monthly SSR and also appended to PBRER No.03. The signals of diarrhoea and dyspnoea remain refuted and will continue to be monitored under routine surveillance, and the signal for tinnitus remains confirmed Addendums for these topics are included in this report.

Retrospective Level 2B case information was downloaded from EudraVigilance for the previously validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus and non-validated signals of angina pectoris, hypertension, herpes zoster and oral herpes. No significant information was received in the L2B downloads that altered the previous disposition of these signals.

Cumulatively, validated signals of anaphylaxis, paraesthesia, myocarditis and pericarditis and tinnitus were confirmed and the CCDS was updated accordingly. Validated and previously evaluated signals of chest pain/chest discomfort, dizziness, encephalitis, encephalomyelitis, menstrual disorders, tachycardia/other rhythm disorders, syncope, acute coronary syndrome associated with hypersensitivity, diarrhoea and dyspnoea have been refuted and closed. These topics will continue to be monitored per routine surveillance.

Summary Evaluation of Important Risks and New Information

During the reporting interval, no new information was received that warranted updates to the safety concerns in the core (EU) risk management plan (RMP).

Overall Benefit-Risk Evaluation

The benefits of Nuvaxovid have been established across the clinical development program and are reflected in the current global labelling. Based on the totality of the data across the SARS-CoV-2 rS clinical development program, NVX-CoV2373 administered as either 2 intramuscular injections at least 21 days (+ 7 days) apart as primary series vaccination or 1 intramuscular injection at approximately 6 months after the completion of primary series vaccination 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 both neutralising antibody titers and cellular immune responses.

In addition, the consistency of immunogenicity and safety of 3 different lots of NVX-CoV2373 in previously vaccinated adult participants has been well demonstrated in a Phase 3 study, 2019nCoV-307 that is completed during the reporting interval, suggesting that NVX-CoV2373 is immunogenic regardless of whether it is used as a first booster or later booster dose, and whether it follows earlier doses of NVX-CoV2373 or other authorized vaccines. Additionally, it displayed immunogenicity against all 3 tested variants of SARS-CoV-2 (Wuhan strain, BA.1 and BA.5 subvariants).

Nuvaxovid has an acceptable safety profile.

For the cumulative period up to 19-Jun-2023, signals of anaphylaxis, myocarditis and pericarditis, paraesthesia/hypoaesthesia and tinnitus have been confirmed. The CCDS has been updated to include anaphylaxis in Section 4.4 (special warnings and precautions for use) and paraesthesia/hypoaesthesia and tinnitus in Section 4.8 (undesirable effects). 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).

Important risks that are recognised with Nuvaxovid include myocarditis and/or pericarditis (important identified risk) and 'Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease' (important potential risk). The EU RMP was updated during the reporting interval to V 3.1 (dated 06-Feb-2023) with no change in the summary of safety concerns. The important potential risks and missing information are managed with routine risk minimisation measures as outlined in the Product Information (as applicable) and monitored via routine and additional pharmacovigilance activities described in the EU RMP. There are no safety concerns requiring additional risk minimisation measures.

Conclusion

During the reporting interval, NVX has received additional authorisations for heterologous booster indication. Anaphylaxis, myocarditis and pericarditis are included in special warnings and precautions and paraesthesia/hypoaesthesia and tinnitus are included as undesirable side effects in the CCDS.

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 V 7.0, dated 02-Feb-2023) for Nuvaxovid. The data contained within this report support the conclusion that the overall benefit-risk balance for Nuvaxovid continues to remain positive.

NVX will continue to monitor the safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines.

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List of Abbreviations

Acronym	Abbreviation Definition
µg	Micrograms
ACCESS	The vACCine COVID-19 monitoring readinESS Project
ACE2	Angiotensin Converting Enzyme 2
ADR	Adverse Drug Reaction(s)
AE	Adverse Event
AESI	Adverse Event(s) of Spec ial Interest
Anti-N	Antinuclear capsid protein
ARGUS	Analytical Reports Gathering and Updating System
BALB/c	Albino, Laboratory-Bred Strain of the house Mouse, MHC Haplotype $H2^d$
BC	Brighton Collaboration
BEST	Biologics Effectiveness and Safety
BLA	Biologics License Application
BNT	BNT162b2 Pfizer–BioNTech
BODIPY	Boron-Dipyrromethane
BSSR	Bi-monthly Summary Safety Report
CBER	Centre For Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
ChAd	ChAdOx1 nCoV-19, AstraZeneca
CI	Confidence Interval
CIC	COVID-19 and Influenza Combination
CIOMS	Council for International Organisation of Medical Sciences
CMA	Conditional Marketing Authorisation
COVID 19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CVE	COVID-19 Vaccine Effectiveness
DIBD	Development International Birth Date
DLP	Data Lock Point
DNA	Deoxy ribonucleic acid
ECDC	European Center for Disease Prevention and Control
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency

Acronym	Abbreviation Definition
EoS	End of Study
EU	European Union
EU SmPC	European Summary of Product Characteristics
EUA	Emergency Use Authorisation
EUL	Emergency Use Listing
EU-RMP	European Union Risk Management Plan
EVDAS	EudraVigilance data analysis system
Fc	Fragment crystallizing
GLP	Good Laboratory Practices
GMEUs	Geometric Mean ELISA Units
GMFRs	Geometric Mean Fold Rises
GMT	Geometric Mean Titer
GVP	Good Pharmacovigilance Practices
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
IBD	International Birth Date
ICC	Influenza COVID Combination
ICD	International Classification of Disease
ICH	International Conference on Harmonisation
ICSR	Individual Case Study Report
ICU	Intensive Care Unit
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IFN γ	Interferon Gamma
IM	Intramuscular(ly)
IME	Important Medical Event
J-NDA	Japanese New Drug Application
KDCA	Korean Disease Control and Prevention Agency
LL	Line Listing
LLT	Lowest Level Term(s)
m1273	mRNA-1273, Moderna
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter(s)
mRNA	Messenger Ribonucleic Acid
n	Number

Acronym	Abbreviation Definition
NA or N/A	Not Available or Not Applicable
NDS	New Drug Submission
NAb	Neutralising antibody titers
NLS	Noble Life Sciences
NVX	Novavax, Inc.
NVX, CZ	Novavax, Czech Republic
O/E	Observed vs Expected
OOS	Out of Specification
OUHSC	University of Oklahoma Health Sciences Center
PAES	Post-Authorisation Efficacy Studies
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
pH	Potential of Hydrogen
PLWH	Persons Living with HIV
PRAC	Pharmacovigilance Risk Assessment Committee
PSAR	Pandemic Special Access Route
PSUR	Periodic Safety Update Report(s)
PT	Preferred Term(s)
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement(s)
qNIV	Quadrivalent Nanoparticle Influenza Vaccine
r	Recombinant
ROR	Reporting Odds Ratio
RR	Rate Ratio
RSI	Reference Safety Information
S	Spike
SAE	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	System Organ Class

Acronym	Abbreviation Definition
SPEAC	Safety Platform for Emergency vACcines
SRT	Safety Review Team
SSI	Significant Safety Issue
SSR	Summary Safety Report
TEAEs	Treatment Emergent Adverse Events
TGA	Therapeutic Goods Administration
TTO	Time to Onset
TNF α	Tumor Necrosis Factor Alpha
UAE	United Arab Emirates
UK	United Kingdom
UMSOM	University of Maryland school of medicine
USA	United States of America
USA FDA	United States of America Food and Drug Administration
USG	United States Government
V	Version
VS	Versus
WHO	World Health Organisation
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the third Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid™ (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) recombinant (r), Spike Protein (S), adjuvanted; also referred to as NVX-CoV2373, interchangeably in the document) compiled for Health Authorities summarising the interval and cumulative safety data received by Novavax (NVX) for the interval 20-Dec-2022 to 19-Jun-2023. This PBRER follows: the International Conference on Harmonisation (ICH) E2C_Harmonised Tripartite Guideline PBRER; European Medicines Agency (EMA) E2C guideline on PBRER; the EMA Module VII Guideline on Good Pharmacovigilance Practices (GVP) – Periodic Safety Update Report; and EMA Guideline on the Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases.

The periodicity of this PBRER is based on the European Union (EU) harmonised birth date (international birth date), which is 20-Dec-2021.

Nuvaxovid is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. Nuvaxovid is authorised as a two-dose primary series and as a booster in individuals 12 years of age and older (authorised as Covovax™ for individuals 7 years and older in India). Nuvaxovid is a purified full-length SARS-CoV-2 rS protein that is stabilised in its prefusion conformation. The addition of the saponin-based Matrix-M™ adjuvant facilitates activation of the cells of the innate immune system, which enhances the magnitude of the S protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies, which may contribute to protection against COVID-19. The prototype SARS-CoV-2 rS nanoparticle vaccine (NVX-CoV2373) developed by NVX is constructed from the full length wild-type SARS-CoV-2 S glycoprotein based upon the original Wuhan-Hu-1 strain and administered with the saponin-based adjuvant Matrix-M for enhanced immunogenicity.

Nuvaxovid is a dispersion for intramuscular (IM) injection. One dose (0.5 milliliters [mL]) of Nuvaxovid contains 5 micrograms (µg) of the SARS-CoV-2 rS protein (produced by recombinant deoxyribonucleic acid [DNA] technology using a Baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda* species) with 50 µg of the Matrix-M adjuvant. Matrix-M contains Fraction-A (42.5 µg) and Fraction-C (7.5 µg) of *Quillaja saponaria* Molina extract per 0.5 mL dose.

Nuvaxovid is supplied as a multi-dose container of 10 doses or 5 doses (of 0.5 mL each). The dispersion is colorless to slightly yellow, clear to mildly opalescent with a pH of 7.2. Nuvaxovid should be stored at 2°C to 8°C.

The primary series of Nuvaxovid is two doses (0.5 mL each) given 3 weeks apart. A booster dose of Nuvaxovid (0.5 mL) may be administered approximately 6 months after completion of

the primary series in adults 18 years of age and older and at least 5 months after completion of the primary series in adolescents 12 through 17 years of age.

Further details on the mechanism of action, indications, pharmaceutical form(s) and instructions for use are presented in the Company Core Data Sheet (CCDS) in Appendix 1.

Specific requirements for countries/region are presented for Australia in Appendix 14, Canada in Appendix 15, the EU in Appendix 16, the United Kingdom (UK) in Appendix 17 and United States of America (USA) in Appendix 18.

2 WORLDWIDE MARKETING AUTHORISATION STATUS

SARS-CoV-2 rS is currently authorised as Nuvaxovid and Covovax in multiple countries, in the EU region and by the World Health Organisation (WHO), an agency of the United Nations, for active immunisation to prevent COVID-19 caused by SARS-CoV-2. Nuvaxovid is authorised as a primary series vaccine and as a booster in individuals 12 years and older. In India, Covovax is additionally authorised as a primary series vaccine for individuals 7 years and older.

In order to fulfill Pharmacovigilance (PV) requirements across regions, NVX has entered into Pharmacovigilance Agreements (PVAs) with Biocelect (Australia, New Zealand), SK Bioscience (South Korea), PharmEng Technology Pte Ltd. (Singapore), Future Health Pharma GmbH (Switzerland), Takeda (Japan); Gulf Med Medicines (United Arab Emirates), Dor Pharmaceutical Services (Israel) and Serum Institute of India Pvt Ltd. (SIIPL), (Bangladesh, India, Indonesia, Philippines, South Africa and Thailand). In addition, the WHO has granted authorisation for both Nuvaxovid and Covovax. Refer to Appendix 3, Table 35 for the Worldwide Marketing Authorisation (WWMA) Status.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

A potential Significant Safety Issue (SSI) was reported to the Australian Therapeutic Goods Administration (TGA) on 05-Apr-2023 concerning a potential out of specification (OOS) on relative potency for Nuvaxovid 10-dose vials distributed solely to the Australian post-authorisation market (batch 4302MF031; 3,236,200 doses). On 05-May-2023, TGA confirmed that they did not consider the OOS to be an SSI. No product complaints or adverse events (AEs) related to potency/lack of effect have been received for this lot. The batch was conservatively recalled on 28-Apr-2023 as a Class II level recall and the OOS result was confirmed on investigation at 69 to 78% against a specification of 81 – 85 %. No other Nuvaxovid batches were impacted, and the recall has been completed.

No other actions were taken for safety reasons during the reporting interval.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the CCDS, Version (V) 6.0, effective date 10-Aug-2022 (refer to Appendix 2).

4.1 Safety Variations

During the reporting interval, NVX has submitted the following safety variations:

- For the addition of anaphylaxis, hypo/paraesthesia and myocarditis/pericarditis labeling update
    - Ministry of Health and Prevention, United Arab Emirates
    - Taiwan Food and Drug Administration
- For the addition of tinnitus labeling update
    - United States Food and Drug Administration
    - European Medicines Agency
    - Medicines and Healthcare Products Regulatory Agency- UK
    - Health Canada
    - Australia Therapeutic Goods Administration
    - New Zealand Medicines and Medical Devices Safety Authority
    - Swiss Medic

During the reporting interval, NVX has received the following safety variation approvals:

- Ministry of Health and Prevention, United Arab Emirates and Taiwan Food and Drug Administration for the addition of anaphylaxis, hypo/paraesthesia
- European Medicines Agency, Health Canada, Australia Therapeutic Goods Administration, Ministry of Health and Prevention, United Arab Emirates, and Taiwan Food and Drug Administration for addition of myocarditis/pericarditis
- Australia Therapeutic Goods Administration, New Zealand Medicines and Medical Devices Safety Authority, and Medicines and Healthcare Products Regulatory Agency-UK MHRA for the addition of tinnitus labeling update

4.2 Summary of Changes to CCDS

During the reporting interval, CCDS V 6.0 was updated to V 7.0 (effective date 02-Feb-2023). A summary of changes in V 7.0 is presented in Table 1 below.

The current version of CCDS in effect at the end of reporting interval is V 7.0, (effective date 02-Feb-2023) and was used to assess individual case safety reports (ICSRs) in the global vaccine safety database for listedness (refer to Appendix 1).

Table 1: Summary of Changes to CCDS

CCDS Version	Approval Date	Summary of Changes
V 7.0	02-Feb-2023	Sections 4.2, 4.8 and 5.1 (dosing and method of administration, undesirable effects and pharmacodynamic properties) were updated with adolescent booster language. New safety and efficacy information was included in support of adolescent booster dosing. Section 4.8 (undesirable effects) was updated to include Tinnitus safety update. Tinnitus was included under Ear and Labyrinth disorders as an undesirable side effect under post-marketing experience. Section 6.5 (nature and contents of container) was updated to include additional drug product presentation (5-dose vial).

5 ESTIMATED EXPOSURE AND USE PATTERNS

The exposure data from the clinical development program and post-authorisation use of SARS-CoV-2 rS are presented below.

5.1 Cumulative Subject Exposure in Clinical Trials

The cumulative number of participants from ongoing and completed clinical trials exposed to SARS-CoV-2 rS, placebo and/or active comparator during the clinical development are summarised in Section 5.1. The exposure from two studies involving COVID-19 and Influenza Combination (CIC) vaccine, 2019nCoV-ICC-E-101 and 2019nCoV-CIC-E-201, are also included in the overall exposure since they have SARS-CoV-2 rS, treatment arms as part of their study designs. Actual treatment exposure for ongoing blinded studies can be estimated based on enrollment and randomisation schemes.

Cumulatively, as of the data lock point (DLP) (19-Jun-2023), 47,395 (45,238 adults and 2,157 paediatric) participants have received at least one dose of SARS-CoV-2 rS in the clinical development program. There are another 3,836 (1,571 adults and 2,265 paediatric) participants involved in blinded studies with a SARS-CoV-2 rS arm.

Table 2 and Table 3 present cumulative number of participants exposed to SARS-CoV-2 rS from ongoing and completed clinical trials, from the Development International Birth Date (DIBD) (23-Apr-2020) to the DLP of this PBRER.

Table 2: Cumulative Exposure in Adult Participants Stratified by Sex and Treatment

Treatment	Number of Adult Participants Exposed (≥ 18 years of age) [a]		
	Male	Female	Total
SARS-CoV-2 rS	23,392	21,846	45,238
Placebo (normal saline)	4,302	4,083	8,385
Blinded *	701	870	1,571
ICC (qNIV + NVX-CoV2373)	212	346	558
Total	28,607	27,145	55,752

[a] Includes final study data from 2019nCoV-101 (Part1), 2019nCoV-302, 2019nCoV-307, 2019nCoV-501 and 2019nCoV-ICC-E-101 studies and study data from ongoing 2019nCoV-101 (Part2), 2019nCoV-301 Adult, 2019nCoV-311, 2019nCoV-505, and 2019nCoV-CIC-E-201 studies. Participants from 2019nCoV-312 study are excluded as they are a subset of 2019nCoV-307 study.

* Includes blinded data from 2019nCoV-CIC-E-201 study

Table 3: Cumulative Exposure in Paediatric participants Stratified by Sex and Treatment

Treatment	Number of Paediatric Participants Exposed (< 18 years of age) [a]		
	Male	Female	Total
SARS-CoV-2 rS	**1131**	**1026**	**2157**
Placebo (normal saline)	**41**	**34**	**75**
Blinded *	**1157**	**1108**	**2265**
Total	2329	2168	4497

[a] Includes data from ongoing 2019nCoV-301, adolescent sub-study and 2019nCoV-503 study.
* Includes blinded data from 2019nCoV-503 study

Table 4 and Table 5 below present cumulative summary tabulations of exposure from clinical trials stratified by age, sex, treatment and racial/ethnic groups.

Table 4: Cumulative Exposure Stratified by Age, Sex and Treatment

Age Range [a]	Male				Female				Grand Total
	SARS-CoV-2 rS	Placebo	Blinded *	ICC	SARS-CoV-2 rS	Placebo	Blinded *	ICC	
6 months – < 24 months	0	0	54	0	0	0	46	0	100
2 – < 6 Years	0	0	470	0	0	0	435	0	905
6 – < 12 Years	0	0	633	0	0	0	627	0	1,260
12 – < 18 Years	1,131	41	0	0	1,026	34	0	0	2,232
18 – 34 Years	6,680	750	0	0	5,758	687	0	0	13,875
35 – 50 Years	7,320	967	16	15	7,015	971	21	22	16,347
51 – 65 Years	6,559	1,409	406	155	6,602	1,470	536	277	17,414
> 65 Years	2,833	1,176	279	42	2,471	955	313	47	8,116
Total	24,523	4,343	1,858	212	22,872	4,117	1,978	346	60,249

[a] Excludes participant data from 2019nCoV-312 study as the participants are a subset of 2019nCoV-307 study
* Includes blinded data from 2019nCoV-503 and 2019nCoV-CIC-E-201 studies

Table 5: Cumulative Exposure in Paediatric and Adult Participants from Clinical Trials Stratified by Racial/Ethnic Group

Racial group [a]	SARS-CoV-2 rS	Placebo	Blinded *	ICC
American Indian or Alaska Native	1,845	199	35	1
Asian	1,896	314	217	9
Black of African American	7,565	598	647	0
Native Hawaiian or Other Pacific Islander	85	5	18	1
White	34,376	7,224	1913	538
Multiple	734	63	10	4
Not Reported	304	42	23	0
Missing	18	3	62	0
Other	162	12	904	5
African	295	0	0	0
Khoisan	87	0	0	0
South African Coloured	5	0	0	0
Aboriginal Australian	23	0	7	0
Total	47,395	8,460	3,836	558

[a] Excludes participant data from 2019nCoV-312 study as the participants are a subset of 2019nCoV-307 study
* Includes blinded data from 2019nCoV-503 and 2019nCoV-CIC-E-201 studies

5.2 Cumulative and Interval Patient Exposure in the Post-Authorisation Setting

Exposure data are derived from administration and distribution data where these data are available to NVX. The regional sources of administration and distribution data, including cut-off dates, are presented in Table 6. Administration data stratified by dose number and age group are provided in Table 9. Distribution data are provided for all regions that received NVX-CoV2373 and Covovax, including some countries/regions where administration data were also available (refer to Table 10).

During the reporting interval, 314,830 NVX-CoV2373 doses were administered across Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, UK and the USA and 14,414 Covovax doses were administered in India. A total of 9,790,300 NVX-CoV2373 doses (9,784,700 NVX-CoV2373 and 5,600 Covovax doses) were distributed globally (refer to Table 10 for interval administration and distribution data).

Cumulatively, as of 19-Jun-2023, 2,872,381 NVX-CoV2373 doses were administered in Australia, Canada, EU, Germany, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, UK and the USA and 41,762 Covovax doses were administered in India. A total of 112,787,170 NVX-CoV2373 doses (103,452,920 NVX-CoV2373 and 9,334,250 Covovax doses) were distributed globally (refer to Table 10 for cumulative administration and distribution data).

Table 6: Sources of NVX-CoV2373 Administration and Distribution Data by Country

Country	Administration Data Source	Administration Data Cut-Off Date	Distribution Data Source	Distribution Data Cut-off Date
Countries Included in O/E Analysis				
Australia [a, d]	COVID19VaccineData@Health.gov.au	11-Jun-2023	Novavax Global Sales	16-Jun-2023
Canada [a]	https://health-infobase.canada.ca/covid-19/vaccine-administration/	19-Jun-2023 [c]	Novavax Global Sales	16-Jun-2023
EU [a]	https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea	19-Dec-2023 [c]	Novavax Global Sales	16-Jun-2023
Germany	https://github.com/robert-koch-institut/COVID-19-Impfungen_in_Deutschland/blob/master/Aktuell_Deutschland_Bundeslaender_COVID-19-Impfungen.csv	27-Apr-2023 [c]	Novavax Global Sales	16-Jun-2023
Japan [a]	Takeda Pharmaceutical Company	11-Jun-2023	Takeda Pharmaceutical Company	11-Jun-2023
New Zealand [a]	https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-vaccine-data	02-May -2023	Novavax Global Sales	16-Jun-2023
Singapore [a]	Singapore Health Sciences Authority	31-Dec-2022	Novavax Global Sales	16-Jun-2023
South Korea	https://ncv.kdca.go.kr/vaccineStatus.es?mid=a11710000000 KDCA COVID-19 Weekly Safety Report	21-May-2023	SK Bio Distribution Data	31-Jan-2023
Switzerland [a]	https://opendata.swiss/en/dataset/covid-19-schweiz	19-Jun-2023 [c]	Novavax Distribution Department	16-Jun-2023
Taiwan [a]	https://www.cdc.gov.tw/Category/Page/9jFXNbCe-sFK9EImRRi2Og	10-Jun-2023	Novavax Global Sales	16-Jun-2023
UK [a]	Communication from Vaccine Delivery Team Gov.UK	29-May-2023	Novavax Global Sales	16-Jun-2023
USA [a]	https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc/data	19-Jun-2023 [c]	Novavax Global Sales	16-Jun-2023

Table 6: Sources of NVX-CoV2373 Administration and Distribution Data by Country

Countries Not Included in O/E Analysis				
Country	**Administration Data Source**	**Administration Data Cut-Off Date**	**Distribution Data Source**	**Distribution Data Cut-off Date**
Bangladesh [b]	http://103.247.238.92/webportal/pages/covid19-vaccination-update.php	N/A	SIIPL	15-Feb-2023
India [b]	https://dashboard.cowin.gov.in/	19-Jun-2023	SIIPL	15-Feb-2023
Indonesia [b]	N/A	N/A	SIIPL	15-Feb-2023
Israel [a]	Israeli Ministry of Health	24-May-2023	Novavax Global Sales	16-Jun-2023
Philippines [b]	https://www.fda.gov.ph/list-of-fda-issued-emergency-use-authorisation/	N/A	SIIPL	15-Feb-2023
South Africa	N/A	N/A	SIIPL	15-Feb-2023
Thailand [b]	N/A	N/A	SIIPL	15-Feb-2023
UAE [a]	N/A	N/A	Novavax Global Sales	N/A

Note: Not Applicable (N/A) indicates source data was unavailable for a given territory or region.
O/E: Observed to Expected
[a] NVX-COV2373
[b] COVOVAX
[c] Cut-off date is not reported by Canada, Germany, Switzerland, USA and European Center for Disease Prevention and Control (ECDC). Date presented for Canada, Germany, Switzerland, USA and EU in this table is the date of extraction.

Table 7 below provides detailed information for the actual doses administered, doses estimated to have been administered as well as the total estimated number of doses administered by dose and presented for interval and cumulative periods. Due to the source data provided by Australia and New Zealand, the interval and cumulative total rows in Table 7 are not consistent with the sum of the individual dosing as these two countries provided data where the total dose was higher than the sum of dose 1, dose 2, and booster. A brief description of each column in Table 7 is presented below.

Actual doses administered include administration records by dose number, that have been transcribed directly from the data source (no adjustments or assumptions have been made). The data in this column represent only those countries that had an administration data source listed in Table 6.

Adjusted doses including re-allocated doses include re-distributed doses obtained from reallocation of doses reported beyond primary series of NVX-CoV2373 or unknown dose series and doses reported from unknown COVID-19 vaccine to 1st, 2nd, and booster dose, summed with actual doses administered. This method of redistribution was done for Canada, EU, and USA. The method of re-distribution is described in Appendix 10.

Calculated doses administered include the assumed number of doses administered from countries for which data were not available. The method of calculation used for this calculation is described in Appendix 10.

Total estimated doses administered include the summation of the values in the following columns: "Adjusted doses including reallocated doses" and the column: "Calculated doses administered". That represents the total number of doses estimated from all countries.

Table 7: Interval and Cumulative Estimated Exposure Data (Administered) from Post-Authorisation Experience

Dose	Actual Doses Administered [a]	Adjusted doses including re-allocated doses (from unknown dose number or unknown vaccine) [b]	Calculated Doses Administered [c]	Total Estimated Doses Administered [d]
Interval				
First Dose	45,815	47,369	38	47,407
Second Dose	49,865	51,713	60	51,773
Booster Dose	233,473	235,459	397	235,856
Unknown Dose Number	0	0	0	0
Interval Total [e]	329,244	334,633	495	335,128
Cumulative				
First Dose	643,150	682,106	38	682,144
Second Dose	505,602	530,570	60	530,630
Booster Dose	1,762,617	1,770,773	397	1,771,170
Unknown Dose Number	9	0	0	0
Cumulative Total [e]	2,914,143	2,986,216	495	2,986,711

Table 7: Interval and Cumulative Estimated Exposure Data (Administered) from Post-Authorisation Experience

Dose	Actual Doses Administered [a]	Adjusted doses including re-allocated doses (from unknown dose number or unknown vaccine) [b]	Calculated Doses Administered [c]	Total Estimated Doses Administered [d]

NOTE: Data sources and cut off dates are presented in Table 6 above. The total number of doses administered column may not add to the number of individuals as individuals may receive more than 3 doses.

[a] 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 6 for the list of countries with administration data.

[b] Column represents administration data re-allocated to first, second and booster dose only (refer to calculations above Table 7). 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 6 are presented in this column. For a list of countries for which this re-allocation was applied, refer to text above Table 7

[c] 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 7 and in Appendix 10.

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

[e] The interval and cumulative total is not consistent with the sum of the individual dosing because part of the data presented represents the 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.

Available exposure subsets by demographic category for each country or region are summarised in Table 8.

Table 8: Demographic Data Available from Exposure Data by Country/Region

Country/Region	Sex Data Available (Y/N)	Age Data Available (Y/N)	Format of Age Data (years)
Australia	N	Y **	12 – 49, 50 – 69, 70+
Canada	N	N	Not Applicable (NA)
EU	N	Y	< 18, ALL, 5 – 9, 10 – 14, 15 – 17, 18 – 24, 25 – 49, 50 – 59, 60 – 69, 70 – 79, 80+, < 60, 60+, Unknown
Japan	N	Y	65+
New Zealand	N	Y ***	12 – 49, 50 – 64, 65+
South Korea	N	N	NA
Switzerland	N	Y	10 – 19, 20 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69, 70 – 79, 80+
Taiwan	N	N	NA
UK	Y	Y	12 – 17, 18 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 64, 65+
USA	N	N	NA
Singapore	N	N	NA

Table 8: Demographic Data Available from Exposure Data by Country/Region

Country/Region	Sex Data Available (Y/N)	Age Data Available (Y/N)	Format of Age Data (years)
Israel	N	N	NA

** Australia administration data is only available until 21-Dec-2022.
*** New Zealand dose administration data stratified by age is only available until 31-Dec-2022.

Administration data stratified by age group are provided in Table 9 for countries and regions that provide exposure by age category including Australia (until 21-Dec-2022), the EU, New Zealand (until 31-Dec-2022), Japan, Switzerland, and UK. The results reflect direct summation from these regions only no extrapolations have been made.

Table 9: Interval and Cumulative Administration Data by Age Group from Post-Authorisation Experience

Total Doses Actually Administered [a,b,c,d]			
Dose	**Paediatrics**	**Adults**	**Elderly**
Interval			
First Dose	6	404	927
Second Dose	38	590	1,250
Third/Booster Dose	21	1,982	5,702
Interval Total	65	2,976	7,879
Cumulative			
First Dose	160	153,250	22,149
Second Dose	162	111,944	18,107
Third/Booster Dose	180	118,206	46,209
Cumulative Total	502	383,400	86,465

[a] 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 6 above, with the exception of New Zealand and Australia as age stratified data is only available until 31-Dec-2022 and 21-Dec-2022 respectively.
[b] Some countries in EU did not provide age categories consistently as per European Center for Disease Prevention and Control (ECDC) data, so this table does not cover all doses from ECDC data.
c Australia and New Zealand had administration data in only adolescent and elderly age groups. Japan had administration data for only elderly age groups (65+ years).
[d] Of note, age group stratification is not standardised across countries and regions. Age groups for the EU, Australia, and New Zealand are as follows: Paediatric < 8 years; adults 18 – 69 years; elderly 70 + years. Age stratification for Switzerland is as follows: Paediatric- ≤ 19 years; adults: 20 – 69 years; elderly 70 + years. Japan classifies elderly as 65+ years

Distribution and administration data presented by region are provided below in Table 10. The data has been transcribed directly from the data source (no adjustments or assumptions have been made). For the calculation of stratified Observed/Expected (O/E) analysis, derivations were made, and these calculations are described in Appendix 10. For estimated exposure data included in the calculation of the O/E analysis, and presented for interval and cumulative periods by region, refer to Table 16.

Table 10: Interval and Cumulative Distribution and Administration Data from Post-Authorisation Experience Presented by Region/License Partner

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Interval (20-Dec-2022 – 19-Jun-2023)		
Australia (Biocelect Pty Ltd) [b]	23,451	2,988,500
Canada (NVX) [b]	4,446	Not available
EU (NVX) [b]	5,545	131,100
Germany (NVX) [b]	2,850	3,000,000
India (SIIPL) [c]	14,414	5,600
Indonesia (SIIPL) [c]	Not available	Not available
Israel (Medicalix/Freyr) [b]	15	1,000,000
Japan (Takeda) [b]	49,691	Not available
New Zealand (Biocelect New Zealand Ltd.) [b]	828	252,000
Singapore (PharmaEng Technology Pte Ltd) [b]	22,800	90,000
South Korea (SK Bioscience) [b]	50,931	0
Switzerland (NVX) [b]	459	24,400
Taiwan (NVX) [b]	130,001	797,200
Thailand (SIIPL) [c]	Not available	Not available
UK (NVX) [b]	589	Not available
USA (NVX) [b]	23,224	1,501,500
Nuvaxovid Total	314,830	9,784,700
COVOVAX Total	14,414	5,600
Interval Total	329,244	9,790,300
Cumulative		
Australia (Biocelect Pty Ltd.) [b]	259,000	24,224,800
Canada (NVX) [b]	32,883	9,724,000
EU (NVX) [b]	351,400	22.335,070
Germany (NVX) [b]	160,154	23,404,690
India (SIIPL) [c]	41,762	126,250
Indonesia (SIIPL) [c]	Not Available	9,008,000
Israel (Medicalix/Freyr) [b]	43	1,535,100
Japan (Takeda) [b]	322,886	8,238,590
New Zealand (Biocelect New Zealand Ltd.) [b]	7,867	2,283,800
Singapore (PharmaEng Technology Pte Ltd) [b]	40,873	705,000
South Korea (SK Bioscience) [b]	971,309	2,932,470
Switzerland (NVX) [b]	3,013	526,400

Table 10: Interval and Cumulative Distribution and Administration Data from Post-Authorisation Experience Presented by Region/License Partner

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Taiwan (NVX) [b]	632,494	1,805,200
Thailand (SIIPL) [c]	Not Available	200,000
UK (NVX) [b]	1,264	1,000,000
USA (NVX) [b]	89,195	4,737,800
Nuvaxovid Total	2,872,381	103,452,920
COVOVAX Total	41,762	9,334,250
Cumulative Total	2,914,143	112,787,170

[a] Data presented as recorded.
[b] NVX-COV2373
[c] COVOVAX

6 DATA IN SUMMARY TABULATIONS

The safety data includes summary tabulations of serious adverse events (SAEs) from clinical trials and spontaneous serious and non-serious adverse drug reactions (ADRs) from the post-authorisation phase.

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), V 26.0 was used for the coding of SAEs and ADRs at the end of the reporting interval and V 25.1 at the beginning of the reporting interval.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 4 presents cumulative summary tabulations of SAEs from NVX-sponsored interventional clinical trials from the DIBD (23-Apr-2020) to the DLP (19-Jun-2023) of the PBRER. Data are extracted from the NVX global safety database and may contain unblinded information. Unblinded data may originate from completed clinical trials (end of study unblinding) and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable.

The data are organised by MedDRA System Organ Class (SOC), in the internationally agreed order, then by the MedDRA Preferred term (PT) alphabetically, for the SARS-CoV-2 rS, as well as placebo and comparator arms as applicable.

Note: Novavax acknowledges the challenges with interpretation of the serious clinical case summary tablulation. Regarding the failure of rows to total across columns, challenges arise with cross-over design studies when those studies are unblinded and where the events reported and the time interval between doses and crossover arms does not permit a strict programatic rule for attributing suspect products, such as attribution to the most recently administered active or placebo vaccine dose prior to the event occurrence. In this regard, both active and placebo vaccines may be suspect for an individual event occuring in an individual subject. Attribution of a single suspect product for the generation of a periodic summary tablulation to achieve accurate totals across rows can be accomplished by applying filters to the original data; however, this programatic attribution will result in artificial imbalances across the dataset. Due to the complexity of the study design, these data are analyzed across the clinical development program by study time period, such as pre-crossover, post-crossover and booster, time interval to event onset and across multiple doses of active and placebo products.

In **2019nCoV-101 (Part 1)** study, 131 participants have been randomised and received either SARS-CoV-2 rS with or without Matrix-M adjuvant or placebo. No subject has experienced treatment emergent SAEs in this study.

In **2019nCoV-101 (Part 2)** study, 1,283 participants received either SARS-CoV-2 rS with Matrix-M adjuvant or placebo and a total of 47 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Injury, Poisoning and Procedural Complications, Cardiac Disorders and Infections and Infestations.

In **2019nCoV-301** study, 29,582 adult participants and 2,232 adolescents received either SARSCoV-2 rS with Matrix-M adjuvant or placebo and a total of 2,141 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Infections and Infestations, Cardiac Disorders and Injury, Poisoning and Procedural Complications.

In **2019nCoV-302** study, 15,138 participants received either SARS-CoV-2 rS with Matrix-M adjuvant or placebo and a total of 468 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Infections and Infestations, Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) and Cardiac Disorders.

In **2019nCoV-307** study, 905 participants received SARS-CoV-2 rS with Matrix-M adjuvant and a total of 2 treatment emergent SAEs were reported that fell under the SOCs of Infections and Infestations (number (n)=1) and General disorders and administration site conditions (n=1).

In **2019nCoV-311** study, 1715 participants received SARS-CoV-2 rS with Matrix-M adjuvant (monovalent Omicron subvariant [BA.5 and BA.1] vaccines, monovalent prototype vaccine or bivalent vaccines) and a total of 28 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Infections and Infestations, Cardiac Disorders and Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps).

In **2019nCoV-312** study, 147 participants (a subset of participants from 2019nCoV-307 study) received SARS-CoV-2 rS with Matrix-M adjuvant. No subjects experienced treatment emergent SAEs as of the DLP of this PBRER.

In **2019nCoV-501** study, 4,408 participants received either SARS-CoV-2 rS with Matrix-M adjuvant or placebo and a total of 100 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Infections and Infestations, Injury, Poisoning and Procedural Complications, and Pregnancy, Puerperium and Perinatal Conditions.

In **2019nCoV-503** study, 2,265 participants received either SARS-CoV-2 rS with Matrix-M adjuvant or placebo and a total of 11 treatment emergent SAEs were reported falling under the SOCs of Infections and Infestations, Respiratory, Thoracic and Mediastinal disorders and Injury, Poisoning and Procedural Complications.

In **2019nCoV-505 study**, 383 participants received SARS-CoV-2 rS with Matrix-M adjuvant and a total of 11 treatment emergent SAEs were reported. The SOCs under which the SAEs have been most frequently reported include Psychiatric Disorders and Nervous System Disorders.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

Appendix 5 presents interval and cumulative count of serious and non-serious ICSRs for all spontaneous, regulatory authority, literature, and only serious ICSRs of Non-interventional Studies. All ICSRs received reflect the version valid at the time of DLP, therefore, the case information and number of ICSRs may change from one PBRER reporting interval to the other.

Note: On two separate occasions, 03-Jan-2023 and 02-May-2023, NVX received a legacy, 6-month bolus of AE data up to 16-Jun-2022 and 31-Dec-2022 respectively from South Korea via Korea Institute of Drug Safety and Risk Management through partner SK Bio and these ICSRs have been entered into the NVX global safety database before the DLP. This data had been previously evaluated in aggregate based on cumulative safety data summaries provided by the Korean Disease Control and Prevention Agency (KDCA) in Section 6.3.1 of PBRER No.02. NVX has reviewed disproportionalities arising from the addition of South Korean data to the global safety database and no new signals have been identified, aligning with findings from prior reviews of the KDCA COVID-19 Vaccine Weekly Summary Reports. The most recent KDCA report (Week 116; data from 26-Feb-2021 to 21-May-2023) has been reviewed and is discussed in Section 6.3.1 below.

The breakdown below is a complete review of all post-authorisation ICSRs in the database that were received during the interval and cumulative periods.

During the 6-month reporting interval, 1,679 spontaneous ICSRs were received (of which 92 ICSRs were follow-ups), with 5,089 AEs (601 serious unlisted AEs, 199 serious listed AEs, 1,517 non-serious unlisted AEs, and 2,772 non-serious listed AEs). A total of 19 initial fatal ICSRs (16 ICSRs from South Korea) were reported during the reporting interval.

Cumulatively, 4,619 spontaneous ICSRs containing 16,710 AEs have been received (of which 808 ICSRs were follow-ups). Of the 4,619 ICSRs received cumulatively, there were 902 serious ICSRs and 3,717 non-serious ICSRs. Of the 16,710 AEs received cumulatively, there were 2,491 serious AEs comprising 1,790 serious unlisted AEs (including 49 fatal AEs), and 701 serious listed AEs, and 14,219 non-serious AEs comprising 6,976 non-serious unlisted AEs and 7,243 non-serious listed AEs. Cumulatively, 28 fatal ICSRs have been received.

6.3.1 Aggregate Adverse Event Data from South Korea

Nuvaxovid was authorised in South Korea on 12-Jan-2022 as a Biologics License Application by SK Bioscience Co., Ltd. The KDCA publishes the COVID-19 Vaccine Safety Report, which includes cumulative aggregate safety data for Nuvaxovid. Since up-to-date individual case-level information is not available for downloading into the NVX safety database, the aggregate data is reviewed separately.

This section summarizes cumulative aggregate safety data from the COVID-19 Vaccine Safety Report [KDCA 2022] (Week 116) covering the period from 26-Feb-2021 to 21-May-2023. A

total of 971,309 Nuvaxovid doses were administered cumulatively as of 21-May-2023, with a corresponding total of 1,279 AEs.

Note: The bolus of AEs entered into the NVX global safety database from the Korea Institute of Drug Safety and Risk Management database represented in data analysis sections of this document have an initial receipt date up to 31-Dec-2022. Because aggregate data from the KDCA reports include safety information up to 21-May-2023, the counts in this section will not align with other sections of the document. NVX will continue to add the South Korea ICSR data from Korea Institute of Drug Safety and Risk Management to the global safety database as it is made available and will also continue to summarize the most up-to-date aggregate data available in this section.

6.3.1.1 Adverse Events in South Korea Following Immunisation by Nuvaxovid Listed by Symptoms

Table 11: Cumulative Number of Cases Reporting Adverse Events/Cases following Administration of Nuvaxovid in South Korea

Symptoms Suspected to be Adverse Events (including duplicates) **	Number of Cases
Myalgia	274
Headache	253
Dizziness	179
Chest pain	171
Allergic reaction	169
Vaccination Site Pain, Rash, Swelling within 3 days of vaccination	134
Queasy	116
Dyspnoea (Breathlessness)	98
Itching	90
Chills	85
Pyrexia	76
Vomiting	53
Cellulitis (Inflammation at the injection site, not an abscess)	39
Abdominal pain	37
Lymph gland infection	32
Diarrhoea	31
Abnormal uterine bleeding	28
Arthritis	27
Severe local adverse reactions	15
Acute paralysis	13
Anaphylactoid reaction	8

Table 11: Cumulative Number of Cases Reporting Adverse Events/Cases following Administration of Nuvaxovid in South Korea

Symptoms Suspected to be Adverse Events (including duplicates) **	Number of Cases
Acute Cardiovascular injuries	7
Vaccine associated enhanced disease	7
Anaphylactic reaction	4
Vaccination site abscess	4
Alopecia *	3
Visual acuity reduced *	3
Encephalopathy or Encephalitis	3
Guillain-Barre syndrome	3
Thrombosis	3
Anosmia	1
Acute aseptic arthritis	1
Acute liver injury	1
Acute renal injury	1
Convulsion (Convulsion/Seizure)	1
Multiple Organ inflammatory syndrome	1

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

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

Four cases of myocarditis (2 males and 2 females, age range 20 – 59 years) meeting a threshold level of diagnostic certainty as defined by KDCA have been identified in the most recent COVID-19 Vaccine Safety Report (Week 116) (Refer to Section 16.3.1.1). Three of the 4 vaccinees experienced the AE of myocarditis after the first dose and the remaining vaccinee experienced this AE after the winter season additional dose.

A review of suspected anaphylaxis cases (including anaphylactoid reaction cases) from 26-Feb-2021 to 28-Apr-2023 was conducted. According to the KDCA report, 6 of the 7 cases were confirmed to have a causal relationship with administration of Nuvaxovid. The age range for 5 of the vaccinees was 30 – 59 years and for the other 2 vaccinees was 19 years of age or younger. Of the 7 vaccinees, 3 vaccinees experienced the AE after the first dose, 1 vaccinee after second dose and 3 vaccinees after the third dose.

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

A total of 18 events in 13 cases were reported as fatal, from a total of 971,309 doses administered as of 21-May-2023. Seven cases concerned males and 6 cases concerned females, with most

cases reported in individuals ages 60 – 79 (n=6). Time from vaccination to death was most frequently reported as ≥ 3 days. Additional case characteristics are summarized in Table 12.

Table 12: Case Characteristics for Fatal Outcomes from South Korea

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

The aggregate data from South Korea is consistent with the known safety profile of NUVAXOVID, and no new signals have been identified.

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

Table 13 below summarizes study populations and study status for NVX-sponsored clinical trials completed or ongoing as of the DLP of this PBRER (19-Jun-2023).

Table 13: Overview of Clinical Trial Status and Population as of DLP (19-Jun-2023)

Study ID	Investigational Vaccine(s)/ Primary Series or Booster	Study Population	Study Status as of DLP
2019nCoV-101 Part 2	NVX-CoV2373 / Primary Series	Healthy participants between 18 to 84 years	ongoing
2019nCoV-301 Main Study Adults	NVX-CoV2373 / Primary Series	Healthy and medically stable adult participants ≥ 18 years	ongoing
2019nCoV-301 Adults	NVX-CoV2373 / Booster	Healthy and medically stable adult participants ≥ 18 years	ongoing
2019nCoV-301 Main Study Adolescents	NVX-CoV2373 / Primary Series	Adolescents 12 to < 18 years	ongoing
2019nCoV-301 Adolescents	NVX-CoV2373 / Booster	Adolescents 12 to < 18 years	ongoing
2019nCoV-302	NVX-CoV2373 / Primary Series	Adults 18 to 84 years	completed
2019nCoV-307	NVX-CoV2373 / Booster	Healthy and medically stable adults 18 to 49 years previously vaccinated against SARS-CoV-2 (primary series with or without booster) at least six months prior to study	completed
2019nCoV-311 Part 1	NVX-CoV2373, NVX-CoV2515[BA.1], or NVX-CoV2373 + NVX-CoV2515[BA.1] / Boosters	Medically stable male and non-pregnant females ≥ 18 and ≤ 64 years	ongoing
2019nCoV-311 Part 2	NVX-CoV2373, NVX-CoV2540 [BA.5], or NVX-CoV2373 + NVX-CoV2540 [BA.1] / Boosters	Medically stable male and non-pregnant females ≥ 18 years	ongoing
2019nCoV-312	NVX-CoV2373 / Primary Series	Medically stable male and non-pregnant female participants who received their first booster of NVX-CoV2373 in Study 307 following prior priming and booster doses with mRNA vaccines.	ongoing
2019nCoV-501	NVX-CoV2373 / Primary Series	Medically stable male and female HIV-positive and healthy adults	completed

Table 13: Overview of Clinical Trial Status and Population as of DLP (19-Jun-2023)

Study ID	Investigational Vaccine(s)/ Primary Series or Booster	Study Population	Study Status as of DLP
2019nCoV-503	NVX-CoV2373 / Primary Series	Children 6 to < 12 years, 2 to < 6 years, and 6 to < 24 months	ongoing
2019nCoV-505	NVX-CoV2373 / Primary Series	People living with HIV (PLWH) and HIV-negative adults 18 to 65 years	ongoing

7.1 Completed Clinical Trials

During the reporting period, three clinical trials were completed: Study 2019nCoV-302, Study 2019nCoV-307, and Study 2019nCoV-501. Potentially relevant, clinically important, emerging efficacy, immunogenicity, and/or safety findings are presented below.

7.1.1 Study 2019nCoV-302

A Phase 3, Randomized, Observer-blinded, Placebo-controlled Trial to Evaluate the Efficacy and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-RS) with Matrix-M1™ Adjuvant in Adult Participants 18 – 84 Years of Age in the United Kingdom

Study 2019nCoV-302, a Phase 3, multicenter, randomized, observer-blinded, placebo-controlled crossover design study evaluating the efficacy, safety, and immunogenicity of a two-dose regimen of NVX-CoV2373 administered 21 days apart, was completed on 17-Jan-2023. The study evaluated 15,187 adult participants 18 to 84 years of age across 33 sites in the UK, with the last subject last visit on 28-Jan-2022. The findings below are summarized from the 2019nCoV-302 Clinical Study Report, V 1.0, 17-Jan-2023.

Efficacy Results

The pre-specified final analysis of the primary efficacy endpoint in support of Emergency Use Authorisation was conducted on 29-Jan-2021, with a median surveillance time of 56.0 days. For this analysis, 10 (0.1%) cases were observed in the NVX-CoV2373 group and 96 (1.4%) in the placebo group, which resulted in a vaccine efficacy of 89.7% (95% confidence interval (CI): 80.2, 94.6; $p < 0.001$). The final analysis of the primary efficacy endpoint in support of the Biologics License Application was conducted on follow-up data through 27-Jul-2021 (6 months after first vaccination of the last participant). The resultant vaccine efficacy of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in serologically negative (to SARS-CoV-2) adult participants at baseline was 82.6% (95% CI: 72.9% – 88.8%), with a lower bound CI greater than 30% meeting the prespecified study success criterion. Relative vaccine efficacy of participants receiving deferred active vaccine (during the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 60.2% (95% CI: 44.8, 71.6). Over the course of the surveillance period, vaccine efficacy

decreased, likely impacted by a surge in resistant COVID-19 variants which are highly immune evasive and evade antibodies from previous infections and vaccinations, in addition to participants' waning immune response.

The vaccine efficacy was 100% (95% CI: -17.9, 100.0) in preventing Polymerase Chain Reaction (PCR)-confirmed symptomatic severe COVID-19 in serologically negative adult participants. Additionally, the vaccine efficacy was 100% (95% CI: 0.000, 37.712) in preventing PCR-confirmed symptomatic moderate or severe COVID-19 requiring hospitalization, Intensive care unit (ICU) admission, or mechanical ventilation in serologically negative adult participants. The vaccine efficacy of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 in baseline seronegative (to SARS CoV-2) adult participants were 85.7% (95% CI: 59.2, 95.0) for the UK (Kent) variant B.1.1.7 and 95.6% (95% CI: 67.7, 99.4) for non-alpha strains.

NVX-CoV2373 demonstrated 82.7% (95% CI, 73.3%–88.8%) efficacy against COVID-19 and 100% (95% CI, 87.0 to 100) against severe COVID-19, at a maximum of 7.5 months post-vaccination in the UK during the first half of 2021 when most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest, largely B.1.1.7 (alpha). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7) [Dunkle 2022].

Safety Results

NVX-CoV2373 was well tolerated across all age cohorts, with nearly 95% of participants receiving both doses of study vaccine. Overall, there were higher frequencies of solicited local and systemic treatment emergent adverse events (TEAEs) among NVX-CoV2373 recipients than among placebo recipients following each vaccination and overall, and in each age cohort. The majority of participants in the NVX-CoV2373 group reported mild, Grade 1 events following the first vaccination and Grade 1 or Grade 2 events following the second vaccination. No new safety signals were detected during the initial vaccination period nor in the crossover period. Therefore, no change in the NVX-CoV2373 safety profile from earlier interim analyses was detected.

7.1.2 Study 2019nCoV-307

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

Study 2019nCoV-307 was a phase 3 study that evaluated the immunogenicity and safety of three different manufacturing lots of NVX-CoV2373 administered across 31 sites in the USA to adults (18 to 49 years) who were vaccinated against SARS-CoV-2 (primary series with or without booster) at least six months prior to this study. Participants were randomized 1:1:1 to receive one dose (5 μg of antigen with 50 μg of Matrix-M adjuvant) of the vaccine from one of the three different lots administered on Day 1. Each lot of NVX-CoV2373 was administered as a single IM injection (Day 1) in a full dose injection volume of approximately 0.5 mL. All participants

remained on study for immunogenicity and safety data collection through 28 days following vaccination. The study evaluated 847 adult subjects for immunogenicity and 865 subjects for safety. This study also explored NVX-CoV2373 immunogenicity as a heterologous booster and as a homologous booster. The first subject-first visit occurred on 11-Jul-2022 and the last subject-last visit occurred on 24-Aug-2023.

The findings below are summarized from the 2019nCoV-307 Clinical Study Report, V 1.0, 10-Mar-2023.

Immunogenicity Results

The primary immunogenicity endpoint was achieved as equivalence was demonstrated for all pairs of NVX--CoV2373 lots as the 95% CIs of Immunoglobulin G (IgG) Geometric mean enzyme-linked immunosorbent assay (ELISA) units (GMEUs) specific for the SARS-CoV-2 S protein (Wuhan) were within the pre-specified equivalence range of 0.67 to 1.5**.**

In participants who received the NVX primary series, neutralizing antibody (NAb) Geometric mean titers (GMTs) following homologous NVX-CoV2373 boosting increased 2.9 -fold in participants with no booster history, 5.8-fold in participants with a NVX booster history and 1.1-fold in participants with a non-NVX booster history. Seroconversion rates (SCRs) were 28.6%, 25.0%, and 0.0%, respectively.

In participants who received the Moderna primary series, NAb GMTs following heterologous NVX-CoV2373 boosting increased 2.3-fold in participants with no booster history, 1.7-fold in participants with a Moderna booster history, and 2.0-fold in participants with other booster history. SCRs were 21.1%, 14.7%, and 16.7%, respectively.

In participants who received the Pfizer primary series, NAb GMTs following heterologous NVX-CoV2373 increased 2.7-fold in participants with no booster history, 2.2-fold in participants with a Pfizer booster history, and 1.7-fold in participants with other booster history. SCRs were 26.3%, 24.1%, and 8.3%, respectively.

Additionally, immunogenicity specific for the SARS-CoV-2 S protein (Wuhan strain) and two Omicron subvariants (BA.1 and BA.5) increased in all participants from Day 1 to Day 29.

NVX-CoV2373 induced robust, broadly reactive humoral responses even against immune-evasive Omicron variants, whether administered as a fully homologous series of NVX-CoV2373 (primary series and first booster) or as a homologous booster.

Safety Results

A single booster dose of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant) was well tolerated in 905 medically stable adult participants. Safety across the 3 lots was comparable and was consistent with the known safety profile of NVX-CoV2373.

NVX-CoV2373 was well tolerated with no new signals identified across the study.

7.1.3 Study 2019nCoV-501

A Phase 2a/b, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M™ Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in People Living With HIV

Study 2019nCoV-501, an observer-blinded, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity at Month 12 of a two-dose regimen of NVX-CoV2373 administered 21 days apart in both primary vaccination and crossover/booster vaccination periods in healthy human immunodeficiency virus (HIV)-negative South African adult participants and medically stable people living with HIV (PLWH) South African participants, was completed on 14-Feb-2023. The study evaluated 4,408 South African healthy participants (≥ 18 to < 85 years) and 245 medically stable PLWH adult participants (≥ 18 to < 65 years). The last patient visit occurred on 13-Aug-2021. The findings below are summarized from the 2019nCoV-501 Clinical Study Report, V 1.0, 14-Feb-2023.

Efficacy Results

A total of 147 symptomatic mild, moderate, or severe COVID-19 cases among all adult participants seronegative (to SARS-CoV-2) at baseline, were accrued for the complete analysis (data extraction 23-Feb-2021), with 51 (3.62%) cases for NVX-CoV2373 versus 96 (7.05%) cases for placebo. The resultant vaccine efficacy of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID19 in adult participants, seronegative (to SARS-CoV-2) at baseline, was 48.6% (95% CI: 28.4, 63.1).

A total of 39 and 186 symptomatic mild, moderate, or severe COVID-19 cases, respectively, among all adult participants seropositive (to SARS-CoV-2) at baseline or regardless of baseline serostatus, were accrued for analysis, with 12 (2.26%) and 63 (3.25%) cases, respectively, for NVX-CoV2373 versus 27 (4.96%) and 123 (6.45%) cases, respectively, for placebo. The resultant vaccine efficacies of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 in all adult participants, seropositive (to SARS-CoV-2) at baseline or regardless of baseline serostatus were, respectively, 54.5% (95% CI: 11.1, 76.7) and 49.7% (95% CI: 32.2, 62.6).

Immunogenicity Results

An initial two-dose regimen of NVX-CoV2373 administered 21 days apart, induced initial robust immune responses through Day 35 that declined over time from Day 35 (pre-crossover) through 201 days after first vaccination, subsequently increased following a third [booster] post-crossover vaccination through Day 236, and then declined from Day 236 through Day 386 (End-of-study [EoS]) in healthy HIV-negative South African participants ≥ 18 to < 85 years of age and medically stable PLWH ≥ 18 to < 65 years of age. Immune responses 35 days following third [booster] post-crossover vaccination rose to levels that were 2.2-, 3.0-, and 2.8-fold higher, respectively, at Day 236 versus those seen at Day 35 and then declined up to 2.7, 3.1-, and 1.9-fold, respectively, from Day 236 through Day 386 (EoS). Despite their decline towards EoS following a third (booster) post-crossover vaccination, immune responses did not return to pre-vaccination levels and remained either slightly below [IgG anti-S antibody], the same as [angiotensin converting enzyme 2 (hACE2) receptor binding inhibition] indicating that immune responses following a booster vaccination were robust. Geometric mean fold rises (GMFRs) for NVX-CoV2373 to booster for all serologically naïve participants were approximately 32, 44, and 57 at Day 236, respectively, demonstrating the effectiveness and durability of a third (booster) dose of NVX-CoV2373, and declined thereafter up to 2.5-, 2.0-, and 2.0-fold, respectively, from Day 236 through Day 386 (EoS).

Ad-hoc analyses of anti-S IgG antibody responses through Month 12 referencing Month 6 (Baseline – Post-Crossover) was performed for the B.1.351 for all participants seronegative or seropositive at baseline or regardless of baseline serostatus. The GMFR for anti-S IgG antibody response for B.1.351 for all serologically naïve participants at Day 236 was approximately 29 NVX-CoV2373 to booster. Anti-S IgG antibody responses for the B.1.351declined 2.4-fold thereafter through Day 386. A similar pattern and magnitude of immune response was seen for serologically naïve HIV-negative participants, indicating the effectiveness and durability of a booster) dose of NVX-CoV2373 against the B.1.351 variant.

Safety Results

Through Month 12 (EoS), a two-dose regimen of NVX-CoV2373, administered 21 days apart (pre-crossover), and a third dose of NVX-CoV2373 administered in a post crossover – booster regimen, were well tolerated in healthy HIV-negative adults (18 to <85 years) and medically stable PLWH (18 to < 65 years), with 96.7% of participants receiving both doses of NVX-CoV2373 (pre crossover) and 97.8% of participants receiving both doses of the post crossover – booster regimen.

Local and systemic reactogenicity were primarily mild to moderate and transient and higher in the NVX-CoV2373 group. Serious adverse events were rare in both groups.

Through EoS from first vaccination, 20 deaths occurred and all but one of the 20 deaths occurred in HIV-negative participants. Ten deaths occurred in the NVX-CoV2373-to-booster group and

10 deaths occurred in the placebo-to-NVX-CoV2373 group. All 20 deaths were assessed as not related to trial vaccine.

7.2 Ongoing Clinical Trials

As of the DLP (19-Jun-2023) for this reporting interval, three clinical trials were ongoing: Study 2019nCoV-101 Part 2; Study 2019nCoV-301; and Study 2019nCoV-311 Parts 1 and 2.

No unexpected new safety information has emerged from the ongoing studies during the reporting interval.

7.3 Long-Term Follow-Up

All 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

During the reporting interval, one compassionate use study was completed in South Africa. This was an open label, randomized, expansion study at participating sites. for up to 300 adult health care workers who were working on the 2019nCoV-501 study. Participants were randomly assigned 1:1 to receive 2 doses of the vaccine, 21 days apart or 56 days apart. This 2019nCoV-501 expansion study enrolled 99 health care workers who were followed for 6 months and collected data outside of Study 2019nCoV-501. Of the 99 enrolled individuals, 87 completed the study. No new clinically relevant safety information was reported from this completed compassionate use study.

7.5 New Safety Data Related to Fixed Combination Therapies

During the reporting interval, a Phase 2, randomised, observer-blind study (Study ID: 2019nCoV-CIC-E-201) to evaluate the safety and immunogenicity of a fixed combination of quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy participants $\geq$ 50 to $\leq$ 80 years of age is ongoing. As of the DLP, 1,571 participants were randomised and no significant safety findings were observed.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

During the reporting interval, 3 Post-Authorisation Safety Studies (PASS) and 2 Post-Authorisation Efficacy Studies (PAES) were ongoing. No significant safety or efficacy 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 5 ongoing investigator-initiated studies, 1 collaborative research study and 3 ongoing license partner sponsored studies. No significant safety findings that would have an impact on the benefit-risk profile of Nuvaxovid were reported from any of these other clinical trials.

Appendix 7, Table 39 summarises studies managed by license partners and Table 40 summarises details regarding ongoing investigator-initiated studies and collaborative research study.

Note: TAK-019-1501 is a license partner-sponsored study that was completed during the PBRER No. 02 reporting interval but was inadvertently presented as an ongoing study in PBRER No. 02. Study TAK-019-1501 is included in Table 39 of completed studies for PBRER No. 03, along with an explanatory note.

9.2 Medication Errors

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

9.2.1 Results and Discussion

A total of 84 ICSRs were retrieved for the interval (79 initial and 5 follow-ups).

Cumulatively, 228 ICSRs were retrieved (91 males, 119 females, 18 individuals of unspecified sex, age range 4 – 94 years when reported). The 228 cumulative ICSRs included 290 medication error related AEs (1 serious and 289 non-serious). The most common PTs reported were Expired product administered (n=37), Inappropriate schedule of product administration (n=30), Incomplete course of vaccination (n=26), Interchange of vaccine products (n=26), Vaccination error (n=21), Product administration error (n=20), Product administered to patient of inappropriate age (n=20), Incorrect product formulation administered (n=19), Incorrect dose administered (n=18), Product storage error (n=17), Wrong product administered (n=16) and Product dose omission issue (n=10). Refer to Appendix 9.

9.2.2 Conclusion

Cumulative evaluation of medication (vaccination) errors did not reveal any particular trend. No new potential safety issues were identified and there is no change to the benefit-risk assessment of Nuvaxovid. Medication (vaccination) errors will continue to be monitored through routine PV activities.

10 NON-CLINICAL DATA

During the reporting interval, there were 5 completed and 15 ongoing non-clinical studies for SARS-CoV-2 rS. There were no significant safety findings from non-clinical studies that impacted the benefit-risk profile of SARS-CoV-2 rS.

Table 14 provides summary of non-clinical studies for SARS-CoV-2 rS that were either ongoing or completed during the reporting interval.

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

Completed Studies				
Study Number & Description (Status)	**Testing Facility (GLP Status)**	**Animals (N)**	**Study Design (Treatment Groups/ Administration/Endpoints)**	**Key Safety Conclusions**
702-087 Cellular and humoral immune responses in baboons **(Final report completed)**	OUHSC (in-life) Novavax (immune response) UMSOM (neutralization) Non-GLP	Olive baboons (n = 2-3/group)	**Immunization with prototype SARS-CoV-2 rS BV2373** 25 µg SARS-CoV-2 rS unadjuvanted 1, 5, or 25 µg SARS-CoV-2 rS + 50 µg Matrix-M1 Administered IM on Days 0 and 21 **Boost with SA B.1.351 SARS-CoV-2 rS BV2426** 3 µg SARS-CoV-2 rS SA B.1.351 + 50 µg Matrix-M1 on Day 318 (all animals) and Day 339 (1-2 animals/group) **Boost with Prototype BV2373 and Omicron SARS-CoV-2 rS BV2509.3 (Day 660 by IM)** 5 µg SARS-CoV-2 rS Omicron BV2509.3 + 50 µg Matrix-M1 (1-2 animals /group) 5 µg SARS-CoV-2 rS prototype BV2373+50 µg Matrix-M1 (1 animal/group)	No safety findings
702-164 SARS-CoV-2 rS Protective efficacy against new variants **(Final report completed)**	UMSOM	BALB/c and K18/hACE2 mice	Prototype BV2373 high dose 1 µg and low dose 10 ng Administered IM on days 0 and 14 Challenge with variants	No safety findings
702-169 T Cell Responses of SARS-CoV-2 rS Omicron BA.2 Variant in Mice. **(Final report completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-6/group)	Homologous prime/boost 1 µg Prototype BV2373 or Omicron BA.2 BV2523 + 5 µg Matrix-M Heterologous prime/boost 1 µg Prototype BV2373/Omicron BA.2 BV2523 + 5 µg Matrix-M Bivalent prime/boost 0.5 µg BV2373+ 0.5 µg Omicron BA.2 BV2523 +5 µg Matrix-M Administered IM on days 0 and 21	No safety findings

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

702-171 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron BA.1, BA.5, and BA.2.12.1 Variants in Mice. **(Final report completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	Homologous prime/boost 0.1 and 1 µg Prototype BV2373, Omicron BA.1, Omicron BA.5, or Omicron BA.2.12.1 + 5 µg Matrix-M Administered IM on days 0 and 14	No safety findings
702-172 T Cell Responses of SARS-CoV-2 rS Prototype, Omicron BA.5, BA.2.12.1 Variants in Mice. **(Final report completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 3-5/group)	Homologous prime/boost 1 µg Prototype BV2373, Omicron BA.5, or Omicron BA.2.12.1 + 5 µg Matrix-M Heterologous prime/boost 1 µg Prototype BV2373 + 5 µg Matrix-M/ Omicron BA.5 + 5 µg Matrix-M Heterologous prime/boost 1 µg Prototype BV2373 + 5 µg Matrix-M/Bivalent 1 µg (Prototype BV2373 +Omicron BA.5) + 5 µg Matrix-M Administered IM on days 0 and 21	No safety findings
Ongoing Studies				
702-115 Long-term immunogenicity & protective efficacy in rhesus macaques **(Ongoing)**	Karolinska Inst	Rhesus Macaques (N=21 Total)	Group 1 and 2 5 µg Prototype BV2373 + 50 µg Matrix-M1 - Week 0 and 4 Booster 5 µg P.1 BV2443 + 50 µg Matrix-M1- Week 35 Challenge WA-1/2020 (group 1), P.1 (group 2)- Week 66 Group 3 and 4 5 µg Prototype BV2373 or P1 BV2443 + 50 µg Matrix-M1 - Week 35 and 39 Challenge P.1 - Week 66	No safety findings

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

702-134 Immunogenicity of Monovalent and Bivalent BA.5 Booster in Baboons- One Year Study **(In-Life completed)**	OUHSC (in-life) Novavax (immune response) Non-GLP	Olive baboons (n = 6/group)	Primary Series administered IM Day 0 and 28 5 µg Prototype BV2373 or Omicron BA.1 BV2515 + 50 µg Matrix-M1 Booster administered IM on Day 150 5 µg Omicron BA.5 or Prototype + BA.5 + 50 µg Matrix-M1	No safety findings
702-149 Evaluation of 6 Month Booster Immunization with Prototype, Omicron BA.1, and Bivalent Vaccines in Rhesus **(In-Life completed)**	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Primary Series administered IM Day 0 and 21 5µg SARS-CoV-2 rS BV2373 + 5 µg MatrixM1 5µg SARS-CoV-2 rS Delta + 5 µg MatrixM1 Booster administered IM on Day 182 5 µg Prototype, BA.1, or Prototype + BA.1 + 50 µg Matrix-M1	No safety findings
702-173 Evaluation of Prototype and Omicron Variants in Rhesus **(Ongoing)**	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Day 0 and 21 Vaccination (IM) (Groups 1-4)- complete 5µg SARS-CoV-2 rS BV2373 + 50 µg MatrixM1 5µg SARS-CoV-2 rS Omicron BA.5 + 50 µg MatrixM1 Bivalent 5µg (2.5 µg each rS) SARS-CoV-2 rS (Prototype BV2373 + Omicron BA.5) + 50 µg MatrixM1 Booster Day 246 ~8 month (Groups 1-4)- complete 5 µg BQ.1.1 or XBB.1.5 with 50 µg Matrix-M1 Primary Series Day 246 and 267 (Groups 5 and 6)- on-going 5 µg XBB.15 with 50 µg Matrix-M Booster (Groups 5 and 6) strain and date TBD Monovalent or bivalent rS	No safety findings

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

702-176 Immunogenicity of SARS-CoV-2 rS Omicron BA.1 GMP DP in mice. **(Analysis completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	0.1µg and 0.5 µg Prototype BV2373 DP GMP, Omicron BA.1 DP GMP, or Omicron BA.1 Discovery 0.1µg and 0.5 µg bivalent (Prototype BV2373 GMP DP+ Omicron BA.1 GMP DP), or bivalent (Prototype BV2373 GMP DP +Omicron BA.1 Discovery) Administered IM on days 0 and 14	No safety findings
702-181 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron BF.7, BQ.1, and BQ.1.1 Variants in Mice. **(Analysis completed)**	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. **(Analysis completed)**	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
702-186 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron BA.2, and XBB.1.5 Variants in Mice. **(Analysis completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	0.1 and 1 µg Prototype BV2373, Omicron BA.2, and XBB.1.5 + 5 µg Matrix-M Administered IM on days 0 and 14	No safety findings

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

702-188 Generation of Prototype and Omicron Variants Antibodies in Mice. **(Analysis completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 20/group)	1 µg Prototype BV2373, Omicron BA.2, BA.5, XBB.1.5 and Prototype + XBB.1.5 + 5 µg Matrix-M Administered IM on days 0 and 14	No safety findings
702-191 Immunogenicity Study 1 in Mice to support Variant Change **(In-Life completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	Primary Series Day 0 and 14- complete 1 µg prototype with 5 µg Matrix-M 1 µg (total rS) bivalent prototype + BA.5 with 5 µg Matrix-M 1 month boost with monovalent rS Day 47- complete 1 µg prototype, BA.5, XBB.1.5, BQ.1.1, CH1.1, XBB1.16 with 5 µg Matrix-M 1 month boost with bivalent rS Day 47- complete 1 µg prototype+BA.5, Prototype+XBB.1.5, Prototype+XBB.1.16, Prototype+BQ.1.1 with 5 µg Matrix-M	No safety findings
702-194 Immunogenicity Study 2 in Mice to support Variant Change **(In-Life completed)**	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	Primary Series Day 0 and 14- complete 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 (11May23) 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	No safety findings
702-196 Immunogenicity of SARS-CoV-2 rS Prototype and Omicron Variants BA.5, XBB.1.5 and XBB.1.16 in mice **(Ongoing)**	NLS (in-life) Novavax (immunogenicity)	BALB/c mice (n = 10-15/group)	Immunization Day 0 and 14 (complete) 1 µg Prototype, BA.5, XBB.1.5, XBB.1.16 with 5 µg Matrix-M Placebo Booster (3 month tentative) with strain and date TBD	No safety findings

Table 14: Summary of Non-Clinical Studies Evaluating SARS-CoV-2 rS

702-198 Generation of antibodies against SARS-CoV-2 rS XBB.1.16 in mice **(In-Life completed)**	NLS (in-life) Novavax (immunogenicity)	BALB/c mice (n = 25)	Immunization Day 0 and 14 1 µg XBB.1.16 with 5 µg Matrix-M	No safety findings
23#353 Visualization of BODIPY-labeled Matrix-M (Fraction-A) in muscle and dLN 0.5 to 24 hours post injection **(In-Life completed)**	SVA Swedish national Veterinary Institute, In life, Novavax, Immunogenicity (Non-GLP)	BALB/c mice (30 or 5 mice/group, females)	Intramuscular injection of fluorescent labeled Matrix-M and/or SARS-CoV-2 rS, collection of injection site and dLN 0.5, 1, 3, 6, 18, 24 hours post injection. Analyzed by flowcytometry. 1. SARS-CoV-2 rS, Alexa Flour 647 labeled, 10µg, 5 animals/time point 2. Matrix-M1 with BODIPY labeled Matrix-A, 5 µg, 5 animals/time point 3. SARS-CoV-2 rS, Alexa Flour 647 labeled, 10 µg + Matrix-M1 with BODIPY labeled Matrix-A, 5 µg, 5 animals/time point 4. SARS-CoV-2 rS, Alexa Flour 647 labeled, 10µg + Matrix-M1 (unlabeled) 5 µg, Control for flowcytometry assay	No safety findings
23#358 Pilot: BODIPY-labeled Fr-C in Matrix-M **(In-Life completed)**	Swedish national Veterinary Institute, In life, Novavax, Immunogenicity (Non-GLP)	BALB/c mice (5 mice/group, females)	Intramuscular injection of fluorescent labeled Matrix-M and/or SARS-CoV-2 rS, collection of injection site and dLN 1 hour post injection. Analyzed by flowcytometry. 1. Matrix-M1, 5 µg 2. Matrix-M1 with BODIPY labeled Matrix-C (10%), 5 µg + SARS-CoV-2 rS, Alexa Flour 647 labeled, 0.1 µg 3. Matrix-M1 with BODIPY labeled Matrix-C (30%), 5 µg + SARS-CoV-2 rS, Alexa Flour 647 labeled, 0.1 µg	No safety findings

Abbreviations: BALB - Albino, laboratory-bred strain of the house mouse, MHC Haplotype H2d, BODIPY - boron-dipyrromethene, GLP - Good Laboratory Practices, GMP - Good Manufacturing Practices, NLS - Noble Life Sciences, OUHSC - Oklahoma University Health Sciences Center, SVA-Swedish national veterinary institute, UMSOM - University of Maryland School of Medicine

11 LITERATURE

During the reporting interval, weekly literature searches were conducted using OVID EMBASE (which includes all of Medline plus over 2,900 extra titles and 3.6 million conference abstracts) to retrieve publications, pre-publication articles in press, unpublished manuscripts, and abstracts presented at medical or scientific conferences that provided new important information on COVID-19 vaccines (e.g., benefits, efficacy, antibody waning, revaccination, need of a booster dose, mixed dose schedule, safety concerns, adverse events of special interests [AESIs]). A total of 194 publications were retrieved and reviewed in their entirety, of which 35 publications presented new, important information. Summaries of the 35 publications are presented below and citations are presented in Appendix 28.

Review of the published peer-reviewed scientific literature and available unpublished manuscripts and conference abstracts did not identify any significant safety findings that impacted the overall benefit-risk balance of NVX-CoV2373.

"Acute Adverse Events at a Mass Vaccination Site after the Third and Fourth COVID-19 Vaccinations in Japan" reported real world data from a study of AEs after the third and fourth doses of COVID-19 vaccines administered at a mass vaccination site in Japan between Dec-2021 and Jul-2022, during which 267,515 individuals received the third, and 32,934 received the fourth COVID-19 vaccine dose. 442 recipients of the third (0.19%), and 22 recipients of the fourth (0.07%) dose reported acute AEs and were examined by doctors on site. NVX-CoV2373 was administered only as a third vaccine dose to 1,953 adults 33 – 50 years of age. Of the 8 overall AEs reported after NVX-CoV2373 administration, there were: 3 events of vasovagal syncope/presyncope; 2 AEs required drug administration and none of the 8 AEs resulted in hospitalization. The incidence of acute allergic reactions appeared to differ between various vaccine manufacturers, whereas that of vasovagal syncope/presyncope did not. These real-world data may benefit the safe and efficient implementation of mass vaccination campaigns for citizens who want to receive COVID-19 vaccines now and in the future [Akaishi 2023].

"Immunogenicity of a Fourth Homologous Dose of NVX-CoV2373" reported new information on the immunogenicity of a fourth homologous dose of NVX-CoV2373. To evaluate the effects of multiple NVX-CoV2373 boosters on vaccine-induced immunogenicity in healthy adults, NVX continued Study 2019nCoV-101 by administering a second booster dose of NVX-CoV2373 after another 6 months. The results showed that boosting with NVX-CoV2373 resulted in enhanced cross-reactive immunity to SARS-CoV-2 variants and induction of a potentially more universal-like response against SARS-CoV-2 variants. No new safety concerns were identified in this study [Alves 2023].

"Safety, Immunogenicity, and Efficacy of the NVX-CoV2373 COVID-19 Vaccine in Adolescents: A Randomized Clinical Trial" evaluated NVX-CoV2373 in adolescents aged 12 to 17 years in an expansion of PREVENT-19, a phase 3, randomized, observer-blinded, placebo-controlled multicenter ongoing clinical trial in the USA (Study 2019nCoV-301 pediatric expansion). In this

phase 3 randomized clinical trial including 2,247 adolescents, neutralizing antibody responses were noninferior compared with those of young adults aged 18 to 25 years Vaccine efficacy was 79.5% and reactogenicity was mostly mild to moderate and transient; no safety concerns were identified. These findings indicated that NVX-CoV2373 was safe, immunogenic, and efficacious in preventing COVID-19 in adolescents, including the predominant Delta variant, . This study had several limitations such as short period of time, and low number of cases that were accrued in each group due to the implementation of the blinded crossover. [Anez 2023].

"Evaluation of a heterologous booster vaccine regimen: Pfizer-BioNTech BNT162b2 mRNA booster vaccine following priming with Novavax NVX-CoV2373" is a conference abstract that reported results from a follow-up observational study of 26 participants in Phase 3 CT of NVX-CoV2373, who subsequently received a Pfizer BNT162b2 booster approximately 7 months or 10.4 months later, which resulted in ~100-fold increase in anti-S IgG against SARS-CoV-2 without any AEs. No participants had prior SARS-CoV-2 infections as determined by anti-N IgG [Babu 2023].

"Anaphylactic reactions after COVID-19 vaccination in Germany" discussed the findings of Paul-Ehrlich-Institute's investigation of confirmed cases of anaphylactic reactions in Germany, concerning subsequent allergy testing and revaccination with a COVID-19 vaccine. The collected data indicated that only a small proportion of cases were Immunoglobulin E (IgE)-mediated reactions (22%) and that a large proportion (73%) of patients could be revaccinated under precautionary measures without recurrence of anaphylaxis. For Nuvaxovid, 2 cases of anaphylaxis, meeting the case definition of Brighton Collaboration levels 1-3, were reported to the Paul-Ehrlich-Institute by the time of evaluation. The author concluded that the pathomechanism of the majority of anaphylactic reactions remains unclear and should be investigated in further studies [Barth 2023].

"Novavax NVX-COV2373 triggers neutralization of Omicron sub-lineages" showed that three doses of NVX-CoV2373 induced high titers of neutralizing antibodies against Omicron BA.1 (GMT: 1,197) and BA.4/BA.5 (GMT: 582), with responses similar in magnitude to those triggered by three doses of an mRNA vaccine and highlighted the potential utility of the NVX-CoV2373 vaccine as a booster in resource-limited environments. The two dose NVX-CoV2373 vaccine regimen elicits robust memory CD4+ and CD8+ T cell responses in 100% and 65% of individuals, respectively. In addition, the two-dose regimen induced antibodies with multiple fragment crystallizing (Fc) -mediated functions, which in non-human primate and human cohorts likely contribute to protection from infection. This T cell and Fc effector function data, which is unlikely to differ following a third dose of the NVX-CoV2373 vaccine, coupled with neutralizing antibodies suggests that this vaccine is likely to prevent severe disease after SARS-CoV-2 breakthrough infection with Omicron BA.4/5 sub-lineages [Bhiman 2023].

"Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico" reported the results of a phase 3, randomized, observer-blinded, placebo-controlled trial in the USA and Mexico during the first half of 2021, to evaluate the efficacy and safety of NVX-CoV2373 in

adults (≥18 years of age) who had not had a SARS-CoV-2 infection. Participants were randomly assigned in a 2:1 ratio to receive two doses of NVX-CoV2373 or placebo 21 days (3 weeks) apart. The primary objective was to determine vaccine efficacy against reverse-transcriptase-polymerase-chain-reaction-confirmed COVID-19 occurring at least 7 days after the second dose. Vaccine efficacy against COVID-19 was 90.4% (95% CI: 82.9 to 94.6; P<0.001). Vaccine efficacy against moderate-to-severe disease was 100% (95% CI: 87.0 to 100). Most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest - largely B.1.1.7 (alpha) (31 of the 35 genomes for variants of concern, 89%). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7). Reactogenicity was mostly mild to moderate and transient but was more frequent among NVX-CoV2373 recipients than among placebo recipients and was more frequent after the second dose than after the first dose [Dunkle 2022].

"Strong CD4+ T-Cell Responses to Ancestral and Variant Spike Proteins Are Established by NVX-CoV2373 SARS-CoV-2 Primary Vaccination" reported results regarding CD4+ T-cell responses to SARS-CoV-2 intact S or pooled peptide stimulation (with ancestral or variant S sequences) , measured via ELISA and intracellular cytokine staining. The results suggested that a clearly discernable spike antigen-specific CD4+ T-cell response was induced after 1 dose, but markedly enhanced after 2 doses. Counts and fold increases in cells producing Th1 cytokines exceeded those secreting Th2 cytokines, although both phenotypes were clearly present. Interferon-γ responses to rS were detected in 93.5% of 2-dose 5-μg recipients. A polyfunctional CD4+ T-cell response was cross-reactive and of equivalent magnitude to all tested variants, including Omicron BA.1/BA.5. The authors concluded that NVX-CoV2373 elicits a moderately Th1-biased CD4+ T-cell response that is cross-reactive with ancestral and variant S proteins after 2 doses [Fries 2023].

"Immediate Adverse Events Following COVID-19 Vaccination in Australian Pharmacies: A Retrospective Review" reported results from a retrospective review of the types and management of immediate AEs following immunization with four COVID-19 vaccines (Comirnaty, Vaxzevria, Spikevax and Nuvaxovid) in Australian pharmacies. For all COVID-19 vaccine brands, the most common immediate AE following immunization was syncope. Pharmacists from 314 (14%) of 2,248 pharmacies who had used the immediate AE following immunisation recording form at least once during the study period were included in the study. Pharmacists in these pharmacies administered 977,559 COVID-19 vaccines, of which there were 11,967 Nuvaxovid vaccine doses. Immediate AEs following immunisation were recorded in 0.05% (n=526/977,559) of all COVID-19 vaccinations. No immediate AEs following immunisation were observed after the Novavax vaccination, aside from syncope after the first dose (n=4/4665, 0.09%) [Gallo 2022].

"Characteristics and outcomes of SARS-CoV-2 breakthrough infections among double-vaccinated and triple-vaccinated patients with inflammatory rheumatic diseases" reported real world data on SARS-CoV-2 breakthrough infections in 551 doubly vaccinated patients (64.6% females) and 803 triply vaccinated patients (71.7% females) with inflammatory rheumatic

diseases, obtained from review of 2,314 records in the German Society for Rheumatology's COVID-19-inflammatory rheumatic diseases registry. Treating rheumatologists voluntarily entered patients' information and treatments, e.g., COVID-19 vaccinations, immunomodulation therapy, co-morbidities, body mass index, and positive PCR-swab test results. The authors' observation period was Feb-2021 to Jul-2022, during which a total of 14 patients received Nuvaxovid (6 as a second vaccination and 8 as a third vaccination). The authors reported they did not observe any relevant differences in the rates of breakthrough infections for the different types of vaccines administered to doubly vaccinated or triply vaccinated patients in this registry. Their findings support triple vaccination for patients with inflammatory rheumatic diseases in this registry, as triple vaccination was associated with lower rates of hospitalization, complications, and fatal outcomes, compared to double vaccination or no vaccination. COVID-19-related hospitalisations were least frequently reported in triply vaccinated patients (2.7%, n=22/803), more frequently reported in doubly vaccinated patients (8.0%, n=44/551), and most frequently reported in unvaccinated patients (15.4%, n=142/923, $\chi^2(p)<0.001$). COVID-19-related complications were least frequently reported in triply vaccinated patients (0.7%, n=6/803), more frequently reported in doubly vaccinated patients (4.2%, n=23/551), and most frequently reported in unvaccinated patients (6.2%, n=57/923) ($p<0.001$). Deaths were least frequently reported in triply vaccinated patients (0.6%, n=5/803), more frequently reported in doubly vaccinated patients (1.8%, n=10/551), and most frequently reported in unvaccinated patients (2.0%, n=18/923) ($\chi^2(p)=0.05$) [Hasseli 2023].

"Safety and Efficacy of the NVX-CoV2373 Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial" reported results on the safety and efficacy of NVX-CoV2373 at completion in the UK of a phase 3 randomised controlled clinical trial of 2 doses of NVX-CoV2373 administered 21 days apart to adults 18 – 84 years. The authors reported new information on safety and efficacy through the end of the placebo-controlled period and previously unreported immunogenicity analyses. A total of 13,989 participants remained in the per-protocol efficacy population (6,989 NVX-CoV2373, 7,000 placebo). At a maximum of 7.5 months (median, 4.5) post-vaccination, there were 24 cases of COVID-19 among the 6,989 NVX-CoV2373 recipients and 134 cases among the 7,000 placebo recipients. Vaccine efficacy against all cases of COVID-19 was 82.7% (95% CI, 73.3% – 88.8%). Vaccine efficacy against severe disease was 100% (95% CI, 17.9%–100.0%). Vaccine efficacy against asymptomatic disease was 76.3% (95% CI, 57.4%–86.8%). High anti-S and neutralization responses to vaccination were evident, together with S-protein–specific induction of interferon-γ secretion in peripheral blood T cells. Incidences of SAEs and AESIs were similar between the two groups. The authors concluded that a 2-dose regimen of NVX-CoV2373 conferred a high level of ongoing protection against asymptomatic, symptomatic, and severe COVID-19 through > 6 months post-vaccination and that the gradual decrease of protection suggested that a booster may be indicated [Heath 2023].

"Calibrated comparison of SARS-CoV-2 neutralizing antibody levels in response to protein-, mRNA-, and vector-based COVID-19 vaccines" provided a direct comparison of the first international SARS-CoV-2 antibody standard, SARS-CoV-2 neutralising antibody response

between three COVID-19: a protein vaccine (NVX-CoV2373), an mRNA vaccine (Comirnaty) and a vector-based vaccine (Vaxzevria). Comparable anti-SARS-CoV-2 potency in sera of NVX-CoV2373 and Comirnaty recipients and the slightly lower levels in response to Vaxzevria were reported as in line with previously published levels of vaccine efficacy, confirmed previous, more indirect approaches and lent further support to the notion that neutralizing antibody responses represent a suitable correlate of protection [Karbiener 2022].

"Reactogenicity, immunogenicity and breakthrough infections following heterologous or fractional second dose COVID-19 vaccination in adolescents (Com-COV3): A Randomised Controlled Trial. Journal of Infection" reported new information on NVX-CoV2373 immunogenicity obtained from a phase II, single-blind, multi-center randomized clinical trial conducted in the UK from Sep-2021 to Nov-2021, during which healthy 12-to-16 years olds received either 30 µg BNT162b2 (BNT-30), 10 µg BNT162b2 (BNT-10), or NVX-CoV2373, eight weeks after a first 30 µg dose of BNT162b2. 37 participants received NVX-CoV2373. No new safety concerns were identified in this study. The new information on immunogenicity was: (1) NVX-CoV2373 following a first dose of 30 µg BNT162b2 elicited robust humoral and cellular immune responses, with higher neutralizing titers against Omicron BA.1 and BA.2 variants than BNT-30; (2) amongst participants naïve to SARS-CoV-2 infection at the time of the second dose, the lowest risk of SARS-CoV-2 infection was observed in the NVX-CoV2373 group, which elicited the highest humoral and cellular immune response overall across the study groups; (3) the highest humoral (including neutralizing antibody titers) and cellular immune responses were observed in the NVX-CoV2373 group and this pattern persisted to day 132 even when participants with SARS-CoV-2 infections following vaccination were excluded from the analysis; (4) the lowest rate of self-reported and serologically confirmed infections was recorded in the NVX-CoV2373 group and the majority of breakthrough infections for the NVX-CoV2373 group occurred later in the study compared to BNT-30 and BNT-10 groups, consistent with the gradual rise in antibody responses from day 132 to day 236 [Kelly 2023]

"A randomized, controlled study to evaluate the safety and immunogenicity of a heterologous booster dose of an adjuvanted SARS CoV-2 recombinant spike protein vaccine in adults" provided the first worldwide report on the safety and immunogenicity of Novavax COVID-19 vaccine manufactured by the Serum Institute of India, SII-NVX-CoV2373. Incidences of unsolicited and solicited AEs were similar between the SII-NVX-CoV2373 and NVX-CoV2373 groups. The vaccine was found safe and well-tolerated. Based on the immune response, SII-NVX-CoV2373 was successfully bridged to NVX-CoV2373 [Kulkarni 2023a].

"Safety and immunogenicity of SII-NVX-CoV2373 (COVID-19 vaccine) in adults in a phase 2/3, observer-blind, randomised, controlled study" reported results from a study of a heterologous booster of Serum Institute of India manufactured COVID-19 vaccine, SII-NVX-CoV2373 (spike protein vaccine) in adults primed with viral vector and inactivated vaccines (ChAdOx1 nCoV-19 or BBV152). All three vaccines were shown to be safe and well-tolerated. The SII-NVX-CoV2373 booster showed numerically better immune responses than BBV152

homologous booster in terms of anti-S IgG, neutralizing antibodies and hACE2 receptor binding inhibition antibodies against a variant of concern (Omicron) [Kulkarni 2023b].

"Immunogenicity and safety of a single booster dose of NVX-CoV2373 (TAK-019) in healthy Japanese adults who had previously received a primary series of COVID-19 mRNA vaccine: Primary analysis report of a phase 3 open-label trial" reported new information on the immunogenicity and safety of a single heterologous booster dose of NVX-CoV2373 in 155 Japanese adults ≥ 20 years who completed a primary series of COVID-19 mRNA vaccines 6 – 12 months before study vaccine. A single heterologous NVX-CoV2373 booster induced rapid and robust anti-SARS-CoV-2 immune responses. The most common local and systemic solicited AEs were tenderness (68.0 %) and malaise (26.0 %), respectively and seven participants (4.7%) reported unsolicited AEs (grade ≤ 2) between vaccination and day 28 [Kuriyama 2023].

"Comparison Of the Effectiveness of Different COVID-19 Vaccines Among PLWH" reported in this conference abstract, their real-world data from the authors' original research on the clinical effectiveness of the third dose of five different COVID-19 vaccines administered to 1,496 persons living with HIV in Taiwan, four of whom received NVX-CoV2373. During the 180 day follow-up period, 297 participants (including 15 (21.7%) who received either MVC-COV1901 or NVX-CoV2373) were diagnosed with COVID-19. Of the 297 participants, 98 patients (6 of whom had received either MVC-COV1901 vaccine or NVX-CoV2373), experienced seroconversion. The authors reported similar rates of new infection with SARS-CoV-2 or seroconversion were observed, regardless the vaccine type for the third dose (log-rank test, p=0.46) [Liu 2023a].

"Persistence of immune responses after heterologous and homologous third COVID-19 vaccine dose schedules in the UK: eight-month analyses of the COV-BOOST trial" reported results from 817 participants in seven study arms of COV-BOOST, a multicenter, randomized, controlled, phase 2 trial of seven COVID-19 vaccines used as a third (booster) dose in the UK: AstraZeneca (Oxford-AstraZeneca), Pfizer (Pfizer-BioNTech), Moderna, NVX, Valneva, Janssen, CureVac. The results suggested that third doses of NVX-CoV2373 compared to BNT (BNT162b2) had a slower humoral decay during the follow-up in both people who had received ChAd/ChAd (ChAdOx1 nCov-19) and those who received BNT/BNT. The absolute titers were significantly higher for BNT than for NVX-CoV2373 for all visits. To note, this study had several limitations such as non-availability of neutralisation data against Omicron variants, enrolling of BNT arm into a fourth dose sub-study and having their eight-month visit approximately one month earlier than other arms [Liu 2023b].

"A linear B-cell epitope close to the furin cleavage site within the S1 domain of SARS-CoV-2 Spike protein discriminates the humoral immune response of nucleic acid- and protein-based vaccine cohorts" reported results from using profiling with peptides derived from the Spike surface glycoprotein of SARS-CoV-2 to compare the antibody reactivity landscapes between patients and different vaccine cohorts. The authors identified an invariant Spike region (amino acids 657-671) N-terminal to the furin cleavage site that elicited a significantly stronger antibody

response in AZD1222 (Vaxzervria) - and BNT162b2 (Comirnaty) - compared to NVX-CoV2373-vaccinees. On the sequence level of the Spike protein, NVX-CoV2373 has a crucial difference to AZD1222 and BNT162b2 in that it carries the 3Q replacement (R682, R683, and R685 switched to Q) that inactivates the furin cleavage site. The rationale for this sequence change was to maximally stabilize the pre-fusion conformation of Spike to raise potent neutralizing antibodies. With respect to the pathways of presentation to the humoral immune system, NVX-CoV2373 protein vaccine is directly exposed together with an adjuvant to immune cells, while adenoviral and mRNA vaccines are taken up by various cell types that eventually express and present Spike protein on their plasma membrane where B-cells can engage it. These differences might, therefore, also play a role in a different B-cell epitope pattern [Lorenz 2023].

"Myopericarditis Associated with the Novavax COVID-19 Vaccine (NVX-CoV2373): A Retrospective Analysis of Individual Case Safety Reports from VigiBase" analyzed the cases of myocarditis and pericarditis in association with NVX-CoV2373 reported to the WHO global database of ICSRs for drug monitoring (VigiBase) by applying disproportionality analyses. Increased disproportionality for myopericarditis was found for NVX-CoV2373 (reporting odds ratio (ROR) 14.47, 95% confidence interval [CI] 11.22 – 18.67) and mRNA vaccines: BNT162b2 (ROR 17.15, 95% CI 16.88 – 17.42) and mRNA-1273 (ROR 6.92, 95% CI 6.77 – 7.08), indicating that NVX-CoV2373 vaccine showed a similar increased disproportionality as mRNA vaccines [Macias Saint-Gerons 2023].

"NVX-CoV2373 vaccine efficacy against hospitalization: A post-hoc analysis of the PREVENT-19 phase 3, randomized, placebo-controlled trial" summarized NVX's post-hoc analysis of hospitalisations in the PREVENT-19 efficacy analysis population, plus additional COVID-19-associated hospitalisations that were excluded from the per-protocol population due to the absence of PCR testing at a central study laboratory to confirm infection. For the per-protocol efficacy analysis population, vaccine efficacy was calculated according to pre-specified disease severity (mild, moderate, or severe) criteria, but the impact on the risk of COVID-19-associated hospitalisation during the analysis period (25-Jan-2021, to 30-Apr-2021 [95 days]), was not specifically investigated. For the per-protocol population, there were 4 total hospitalisations among the 77 events analyzed and all 4 hospitalisations involved placebo recipients, yielding a post-hoc vaccine efficacy against hospitalisation of 100% (95% CI: 28.8, 100). By comparison, post-hoc analysis of the expanded efficacy population which included COVID-19-associated hospitalisations without the required PCR testing at the study central laboratory, showed there were 12 total hospitalisations and all 12 involved placebo recipients, also yielding a post-hoc vaccine efficacy against hospitalisation in the expanded population of 100% (95% CI: 83.1, 100) [Marchese 2023].

"Serological response to Nuvaxovid (NVX-CoV2373) vaccine given as a fifth dose in non- and low-responder kidney transplant recipients" reported the effects of a fifth dose of Nuvaxovid in kidney transplant recipients who had previously received four doses of an mRNA vaccine and had responded with no or low levels of antibodies. Nuvaxovid as the fifth dose induced a high

serological response in 17% (n=5) of the patients. Of the patients who were seronegative before Nuvaxovid, 44% (n=7) seroconverted, but in general to low antibody titers [Nowak 2023].

"Adverse Events Following Immunization (AEFIs) for COVID-19 in Ontario: December 13, 2020 to May 21, 2023" presented a summary of AEs following immunization for COVID-19 in Ontario and indicated that 32 reports of AEs following immunization (all non-serious) were reported after 15,639 doses of Nuvaxovid. The most commonly reported AEs were other severe or unusual events (n=14; unspecified), allergic skin reactions (n=9) and anaesthesia/paraesthesia (n=8). The report suggested that, due to data limitations, the identified adverse events following immunization reports should not be interpreted as causally related with vaccine [Public Health Ontario 2023].

"Immunogenicity and safety of NVX-CoV2373 as a homologous or heterologous booster: A phase 3 randomized clinical trial in adults" reported results from 2019nCoV-307, a phase 3 randomized clinical trial conducted in the United States, evaluating immunogenicity and safety of 3 registration batches of NVX-CoV2373 administered to previously vaccinated adults 18 – 49 years. The new immunogenicity information was that NVX-CoV2373 induced robust IgG and nAb responses when used as a first or as a later booster dose and that the induced antibodies were strongly reactive, even to the immune-evasive Omicron BA.1 and BA.5 variants. No new safety concerns were identified in this study [Raiser 2023].

"Efficacy of mRNA-1273 and Novavax ancestral or BA.1 spike booster vaccines against SARS-CoV-2 BA.5 infection in non-human primates" reported results from a non-human primate study to characterize the magnitude, breadth, and persistence of humoral and cellular immune responses induced by different booster vaccines (mRNA-1273 vaccine, NVX-CoV2373, NVX-CoV2515) in animals originally vaccinated with the two-dose mRNA-1273 primary series. All three booster vaccines induced a strong BA.1 cross-reactive binding antibody with IgG4 dominance and comparable neutralizing and non-neutralizing antibody responses against multiple variants of concern. The ratio of BA.1 to WA-1 spike-specific antibody-secreting cells in the blood was higher in NVX-CoV2515 animals compared to NVX-CoV2373 animals, suggesting a better recall of BA.1 specific memory B cells by the BA.1 spike-specific vaccine compared to the ancestral spike-specific vaccine. Further, all three booster vaccines induced low levels of spike-specific CD4, but not CD8, T cell responses in the blood. Following challenge with SARS-CoV-2 BA.5 variant, all three vaccines showed strong protection in the lungs and controlled virus replication in the nasopharynx. In addition, both Novavax vaccines blunted viral replication in the nasopharynx at day 2. Overall, these results demonstrated that a booster with either the mRNA-1273, NVX-CoV2373, or NVX-CoV2515 vaccine provided protection from virus replication in the lower airway even after 3 months post-vaccination, and a booster with both NVX-CoV2373 and NVX-CoV2515 vaccines provided superior viral control in the upper airway against BA.5 variant of concern infection in non-human primates [Routhu 2023].

"COVID-19 Vaccines and Atrial Fibrillation: Analysis of the Post-Marketing Pharmacovigilance European Database" evaluated the reporting frequency of atrial fibrillation related to COVID-19 vaccines from analysis of European pharmacovigilance data on atrial fibrillation following COVID-19 vaccination. This is a retrospective observational study carried out on data available from the reports of adverse events following immunization related to COVID-19 vaccines in Europe sent from 01-Dec-2020 to 28-Nov-2022 to the regulatory medicine agencies. The study included: mRNA-based vaccines "elasomeran" (Moderna) and "tozinameran" (Pfizer-BioNTech); viral vector vaccines, "AD26.COV2.S" (Janssen) and "ChAdOx1-S" (AstraZeneca); and the recombinant subunit protein vaccine "NVX-CoV2373" (Novavax). NVX-CoV2373 was excluded from the disproportionality analyses since only 2 ICSRs were reported. These 2 ICSRs reported atrial fibrillation after first dose of NVX-CoV2373 and the outcome was reported as recovered and unknown respectively. No other information related to NVX-CoV2373 has been identified. The majority of atrial fibrillation reports were related to mRNA vaccines [Ruggiero 2023].

"COVID-19 vaccination-related adverse events among autoimmune disease patients: results from the COVAD study" reported the safety of COVID-19 vaccines in patients with systemic autoimmune and inflammatory disorders. Overall, vaccination against COVID-19 was safe in systemic autoimmune and inflammatory disorders patients. Although these patients were at a higher risk of major AEs than healthy controls, the absolute risk was small. There were small differences in minor AEs between vaccine types in these patients. COVID-19 vaccination-related AEs and AEs seven days post-vaccination were assessed in the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study, a patient self-reported cross-sectional survey. However, the number of patients with systemic autoimmune and inflammatory disorders who received the Novavax vaccine (n=10; 0.2% of study population) was too small to draw any meaningful conclusions. Two patients who received Nuvaxovid experienced difficulty with breathing and one was hospitalised [Sen 2023].

"Persistence of immune response in heterologous COVID vaccination schedules in the Com-COV2 study - A single-blind, randomised trial incorporating mRNA, viral-vector and protein-adjuvant vaccines" reported results from a single blinded trial in which adults ≥ 50 years (n=1,072), previously immunized with single dose 'ChAd' (ChAdOx1 nCoV-19, AZD1222, Vaxzevria, Astrazeneca) or 'BNT' (BNT162b2, tozinameran, Comirnaty, Pfizer/BioNTech), were randomised 1:1:1 to receive a second dose 8-12 weeks later with either the homologous vaccine, or 'Mod' (mRNA-1273, Spikevax, Moderna) or 'NVX' (NVX-CoV2373, Nuvaxovid, Novavax). Immunological follow-up and the secondary objective of safety monitoring were performed over nine months. The results suggested that heterologous ChAd-primed schedules remain more immunogenic over time in comparison to ChAd/ChAd. Immunisation with BNT/NVX generated a qualitatively different antibody response to BNT/BNT, with the total IgG significantly lower than BNT/BNT during all follow-up time points, but similar levels of neutralising antibodies. BNT-primed schedules with a second dose of either mRNA vaccine also remained more immunogenic over time in comparison to BNT/NVX [Shaw 2023].

"Multiple COVID-19 vaccine doses in CLL and MBL improve immune responses with progressive and high seroconversion" reported that patients with chronic lymphocytic leukemia or monoclonal B-lymphocytosis have impaired response to COVID-19 vaccination. However, the authors concluded that multiple COVID-19 vaccine doses in chronic lymphocytic leukemia and monoclonal B-lymphocytosis patients improve immune responses with progressive and high seroconversion. Vaccination occurred through the Australian government program with Vaxzevria, Comirnaty, Spikevax or Nuvaxovid. Most patients had an initial 2 doses with Vaxzevria, then subsequent doses mostly with Comirnaty vaccine and some with Spikevax. The proportion of patients vaccinated with Nuvaxovid is not clear from the article. Multiple sequential COVID-19 vaccine doses significantly increased serological responses, both seroconversion and higher anti-spike antibody levels, together with neutralizing activities, and resulted in stronger SARS-CoV-2-specific T-cell response in a high proportion of patients with chronic lymphocytic leukemia and in virtually all patients with monoclonal B-lymphocytosis [Shen 2022].

"Safety and immunogenicity of COVID Influenza Combination Vaccine" reported on a CIC vaccine comprising a recombinant SARS-CoV-2 Spike (rS) and quadrivalent influenza hemagglutinin protein nanoparticles (qNIV) and Matrix-M adjuvant. Results from a Phase 1/2 CIC dose-finding trial showed that CIC formulations were well-tolerated and immunogenic, with various dose combinations achieving response comparable to the standalone vaccines [Shinde 2022].

"COVID-19 vaccination efficacy in numbers including SARS-CoV-2 variants and age comparison: a meta-analysis of randomized clinical trials" reported a systematic literature review and meta-analysis of 17 randomized controlled clinical trials for COVID-19 vaccines, of which two publications concerned NVX-CoV2373 (one phase 2a/b trial in South Africa and one phase 3 trial in the UK). The overall efficacy of NVX-CoV2373 against symptomatic COVID-19 infection was 80% and the overall efficacy against severe COVID-19 was 84%. However, efficacy varied considerably between the two countries in which NVX-CoV2373 trials were conducted. Efficacy against symptomatic and severe COVID-19 in South Africa was 60 – 67% where the dominant variant was B.1351. However, efficacy against symptomatic and severe COVID-19 in the UK was 90 – 91% where the dominant where the dominant variant was B.1.1.7 [Sobczak 2022].

"1947. Evaluating the Relationship Between Obesity and the Humoral Immune Response to COVID-19 Vaccines" is a conference abstract that reported the relationship between obesity and the humoral immune response to COVID-19 vaccines and concluded that inflammation may be negatively associated with antibody response to COVID-19 vaccines. Waist circumference and antibody response may be positively related in NVX-CoV2373 recipients, in spite of chronic low-grade inflammation [Tables 2023].

"Evaluating the reactogenicity of COVID-19 vaccines from network-meta analyses" reported in this systematic literature review and network-meta analyses, the relative reactogenicity of COVID-19 vaccines currently approved by EMA (including NVX-CoV2373) following primary series vaccination in this study. NVX-CoV2373 was the second best-tolerated vaccine according to the surface under the cumulative ranking curve score and the median odds ratio estimates for each endpoint. NVX-CoV2373 was estimated to have the highest probability of being the best-tolerated vaccine for arthralgia and nausea/vomiting after the first and second doses. The reduced chance of experiencing an adverse event with some COVID-19 vaccines may help to overcome vaccine hesitancy in population groups with concerns about the side effects of vaccines [Tiozzo 2023]

"Safety and Immunogenicity of the NVX-CoV2373 Vaccine as a Booster in Adults Previously Vaccinated with the BBIBP-CorV Vaccine: An Interim Analysis" reported results from a large randomized clinical trial investigating the safety and immunogenicity of NVX-CoV2373 as a heterologous booster after an inactivated vaccine Sinopharm BIBP COVID-19 vaccine (BBIBP-CorV) utilized as a homologous booster. In the NVX (heterologous) arm, 93 participants (18.6%) had received two prior BBIBP-CorV vaccinations and 405 participants (81.2%) had received three prior BBIBP-CorV vaccinations. In the BBIBP-CorV vaccine arm, 92 participants (18.4%) had received two prior BBIBP-CorV vaccinations and 408 participants (81.4%) had received three prior BBIBP-CorV vaccinations. The results showed there were no new safety concerns for both vaccines, that heterologous boosting with NVX-CoV2373 was a highly immunogenic and safe vaccine regimen after vaccination with BBIBP-CorV, and there were low levels of reactogenicity when NVX-CoV2372 was used a heterologous booster or when BBIBP-CorV was used as a homologous booster [Toback 2023].

"Augmented humoral and cellular immunity against severe acute respiratory syndrome coronavirus 2 after breakthrough infection in kidney transplant recipients who received 3 doses of coronavirus disease 2019 vaccine" presented results from a prospective study in South Korea of the humoral (anti-spike protein Abs) and cellular immune responses (interferon gamma releasing assay) after a third COVID-19 vaccination with an unspecified booster vaccine (mRNA or NVX-CoV2373) was administered to kidney transplant recipients. The study population included 38 non-identifiable immunosuppressed solid organ transplant recipients who previously received kidney transplants, and 38 matched health care workers. Shortly after enrolment, when an Omicron BA.1/BA.2-dominated COVID-19 outbreak occurred, followed by a smaller Omicron BA.5-dminated outbreak, approximately half of each cohort experienced breakthrough infections. Anti–spike protein antibody titers of kidney transplant participants were lower than those of health care workers, but significantly increased after booster vaccines and breakthrough infection. The gap between the 2 groups became narrower from a 90-fold difference to a 2-fold difference and was maintained. The authors' findings wre consistent with previous studies that found vaccine-induced immunity was weak in solid organ transplant whereas the natural infection-induced immune response was comparable to non-immunocompromised hosts [Yang 2023].

12 OTHER PERIODIC REPORTS

Periodic reports submitted to relevant health authorities during the reporting interval by SIIPL (Covovax) and NVX (Nuvaxovid) are detailed in Table 15 below.

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

Table 15: Periodic Summary Safety Reports Submitted to Health Authorities

Periodic Report	Reporting Interval	Submission Countries
Nuvaxovid BSSR No.02	16-Nov-2022 to 15-Jan-2023	EU
Nuvaxovid SSR No. 12	01-Dec-2022 to 31-Dec-2022	USA
Covovax SSR No. 17	01-Jan-2023 to 31-Jan-2023	Serum territories
Covovax PSUR No. 01	16-Aug-2022 to 15-Feb-2023	South Africa
Nuvaxovid SSR No. 13	01-Jan-2023 to 31-Jan-2023	USA
Nuvaxovid SSR No. 14	01-Feb-2023 to 28-Feb-2023	USA
Nuvaxovid SSR No. 15	01-Mar-2023 to 31-Mar-2023	USA
Nuvaxovid SSR No. 16	01-Apr-2022 to 30-Apr-2023	USA
Nuvaxovid SSR No. 17	01-May-2023 to 31-May-2023	USA

SSR: Summary Safety Report, BSSR: Bi-monthly SSR, PSUR: Periodic Safety Update Report, EU: European Union, USA: United States of America
Serum territories: Bangladesh, India, Indonesia, Philippines, South Africa and Thailand

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

The signal of sensorineural hearing loss was validated during the reporting interval following a health authority request (TGA) received on 15-Jun-2023 for safety assessment of this topic. The signal was refuted following assessment, shortly after DLP of this report (on 30-Jul-2023).

During the reporting interval, supplementary information was reviewed for the signals of diarrhoea, dyspnoea and tinnitus, following the receipt of Pharmacovigilance Risk Assessment Committee (PRAC) assessment of the bimonthly summary safety report (SSR) No.02. No changes were made to the previous disposition of these signals after the review and the signals were closed shortly after the DLP. See Section 16.2.

During the reporting interval, additional analyses, reviewing for rechallenge data, on the previously refuted safety signal of menstrual disorders in association with the administration of Nuvaxovid was conducted in response to the request received on 28-Dec-2022 from PRAC pursuant to EMA PRAC assessment of SSR 10 (8th SSR to EMA, first bi-monthly SSR) (period covering 01-Sep-2022 to 15-Nov-2022). No changes were made to the previous disposition of this signal after the review, and the signal was closed. See Section 16.2.

A cumulative tabulation of all new, ongoing or closed signals are presented in Appendix 6, Table 36.

15.2 Requests from Competent Authorities

15.2.1 SwissMedic Requests

15.2.1.1 Tachycardia and Other rhythm abnormalities (Closed Signal)

A signal of tachycardia and other rhythm abnormalities was validated on 27-Jun-2022, pursuant to a PRAC request in their assessment report for the 4th monthly SSR (01-May-2022 to 31-May-2022). The complete signal evaluation did not identify any apparent pattern or trend that would identify specific diagnoses. Additionally, these cases were confounded by concurrent events, some of which may relate to the listed events including hypersensitivity or vaccination anxiety-related events or other topics under review such as myocarditis/pericarditis. This signal was refuted.

Pursuant to Swissmedic's request to discuss tachycardia and rhythm disorders in the following periodic safety update report, NVX reviewed the data and has the following observations.

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

Seventy-one ICSRs were retrieved for the interval (49 initial and 22 follow-up).

Cumulatively, 492 ICSRs were retrieved (359 females, 127 males, 6 individuals of unspecified sex; age range 15 – 86 years when reported). The 492 cumulative ICSRs included 621 AEs of which 3 events were fatal, 236 events were serious, and 382 events were non-serious. The most common PTs reported were coded to PTs Palpitations (n=176), Tachycardia (n=125) and Heart rate increased (n=38). Out of the 236 non-fatal serious events, 5 AEs involved disability, 28 AEs involved hospitalisation only, 1 AE was considered life-threatening, and 202 AEs were designated as serious, meeting important medical event (IME) criteria. Of the 202 AEs that were designated as serious, meeting IME criteria, 3 AEs additionally involved disability, 2 AEs were considered life-threatening, 23 AEs involved hospitalisation, 1 AE was considered life-threatening and involved hospitalisation, 1 AE involved disability, hospitalisation and was considered life-threatening. Of the 621 AEs, 263 AEs were reported as not recovered or not resolved, 129 AEs were reported as recovered, 122 AEs were reported with unknown outcome, 92 AEs were recovering, 12 AEs recovered with sequelae and 3 AEs resulted in a fatal outcome.

No safety signal was identified.

15.2.1.2 Menstrual Disorders (Closed Signal)

A signal of menstrual disorders was validated on 27-Jun-2022, pursuant to a request from PRAC, in their assessment of SSR No.04 (01-May-2022 to 31-May-2022). A complete signal evaluation was performed. Based on a comprehensive review of the available data, including the balance of events in clinical programs, the prevalence of menstrual disorders in the general population, the known association with stress/anxiety, and the limited information in the case reports, this signal was refuted.

A signal of menstrual disorders rechallenge was validated on 28-Dec-2022, pursuant to a PRAC request in their assessment report of the first bi-monthly SSR. The signal was refuted as there is limited data available to determine rechallenge information on menstrual disorders with the use of Nuvaxovid.

NVX received a request from Swissmedic following the assessment of PBRER No.02, to discuss menstrual disorders and the information is presented in Section 15.4.6.

15.3 Adverse Events of Special Interest (AESIs)

The following safety topics, AESIs (not considered as signals) are being closely monitored based on recommendations for COVID-19 vaccines or upon request from health authorities. The global vaccine safety database was queried for AESIs for the cumulative period up to DLP (19-Jun-2023) according to prespecified search strategies (refer to Appendix 12). All retrieved ICSRs were reviewed individually and in aggregate and cumulative O/E analyses were performed up to the DLP.

- Acute Disseminated Encephalomyelitis
- 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
- 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
- Venous Thromboembolism

Methods for AESI Analysis:

Crude O/E calculations are made prior to adjudication of cases for the purpose of signal generation (refer to Appendix 11 for a complete view of O/E tables). Analyses are performed for all AESI for which numerator data has been reported except for AESIs related to pregnancy, since exposure is unknown in Women of Child-Bearing Age. O/E analyses are also not performed for Vaccine Associated Enhanced Disease, as it is not possible to determine an expected count for this medical concept as an exposure to vaccine is necessary to develop this 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). Risk windows are applied according to published recommendations, and in instances where time to onset (TTO) is unknown, cases are conservatively assessed to fall within a given risk window. Based on previous health authority requests, sensitivity analyses on specific risk windows are also conducted for some AESIs.

Furthermore, for dose-specific O/E, to reduce the possibility of double counting an AE for which the TTO falls within the risk window of multiple doses, the TTO is assigned only to the most recent dose number reported for the respective AE.

Following the generation of statistically significant hypothesis generating O/E results, a detailed case series analysis is performed, including adjudication against case definitions, where available, and the assessment of individual case and aggregate causality.

Sources of risk window, background incidence rate, and administration data are presented in Appendix 10. The Confidence Interval (CI) is calculated using the method from Garwood 1936.

The majority of AESI ICSRs are from health authorities and social media sources. For countries with enhanced surveillance programs under emergency use authorisations:

- Where ICSRs are obtained by NVX from health authority websites or databases, including TGA Database of AE Notifications and European Medicines Agency's EudraVigilance database, follow-up queries are not directly issued by NVX. Follow-up is solicited directly from TGA and downloaded from the EudraVigilance data analysis system (EVDAS) for prioritised AESI cases to obtain information necessary for O/E calculations and case adjudication.
- Where ICSRs are not available or available in a limited way to the sponsor, known exposure in that country is either not included, or is included with limitations in O/E calculations for calculation of expected counts. For example, since there are limited ICSRs from South Korea in the safety database reported after 31-Dec-2022, Nuvaxovid doses administered in South Korea after 31-Dec-2022 are excluded from the denominator of O/E. This exclusion is purposely done to prevent immortal time-bias created by the absence of individual case reports after this date from this country. Aggregate data from South Korea is summarised in Section 6.3.1 and Section 16.3.1.1.
- In addition, for some low- and middle-income countries, such as India, there have been limited ICSRs reported to NVX, and it is likely that NVX is not receiving comprehensive safety data that would allow for reliable analyses. For these countries, the ICSRs and exposure data are not included in the O/E analysis to avoid underestimation of the O/E results.

The estimated administration by region used in O/E analysis is presented below in Table 16. For Canada, EU and USA, adjusted unknown vaccine was included in the exposure of O/E based on the proportion of Nuvaxovid vaccines overall. Doses administered in South Korea after 31-Dec-2022 are excluded from O/E calculations, as limited ICSRs from South Korea appear in the safety database reported after 31-Dec-2022. Since administration data from Germany are only available until 07-Apr-2023, the dose number after that were derived. The calculation method for the dose data from Germany is described in Appendix 10.

Summary details on validated signals are presented in Section 15.1.

Table 16: Interval and Cumulative Estimated Administration Data Included in O/E from Post-Authorisation Experience Presented by Region

Region [c]	Reported Doses Administered [e]	Derived Doses Administered	Total Doses Used in the O/E
Interval (20-Dec-2022 to 19-Jun-2023)			
Australia	23,451	Not Available	23,451
Canada [c]	4,446	1	4,447
EU [c]	5,545	5,346	10,891
Germany [a]	2,850	495	3,345
India	14,414	Not Available	0
Israel	15	Not Available	0
Japan	49,691	Not Available	49,691
New Zealand	828	Not Available	828
Singapore	22,800	Not Available	22,800
South Korea [b]	50,931	Not Available	0
Switzerland	459	Not Available	459
Taiwan	130,001	Not Available	130,001
UK	589	Not Available	589
USA [c]	23,224	42	23,266
Interval Total	329,244	5,884	269,768
Cumulative			
Australia	259,00	Not Available	259,000
Canada [c]	32,883	22	32,905
EU [c]	351,400	71,931	423,331
Germany [a]	160,154	495	160,649
India	41,762	Not Available	0
Israel	43	Not Available	0
Japan	322,886	Not Available	322,886
New Zealand	7,867	Not Available	7,867
Singapore	40,873	Not Available	40,873
South Korea [b]	971,309	Not Available	920,378
Switzerland	3,013	Not Available	3,013
Taiwan	632,494	Not Available	632,494
UK	1,264	Not Available	1,264
USA [c]	89,195	120	89,315
Cumulative Total	2,914,143	72,568	2,893,975

Table 16: Interval and Cumulative Estimated Administration Data Included in O/E from Post-Authorisation Experience Presented by Region

Region [c]	Reported Doses Administered [e]	Derived Doses Administered	Total Doses Used in the O/E

[a] Since Germany no longer provides exposure data, assumptions have been made to determine the exposure for the interval period.
[b] Doses administered in South Korea after 31-Dec-2022 are excluded from the denominator of O/E, as limited ICSRs from South Korea appear in the safety database reported after 31-Dec-2022.
[c] Adjusted unknown vaccine was included in the denominator of O/E based on the proportion of NUVAXOVID over all vaccines.
[d] For Bangladesh, India, Indonesia, Israel, Philippines, South Africa, Thailand, and UAE, the ICSRs and exposure data are not included in the O/E analysis.
[e] Data presented as recorded.

General Limitations of Global O/E Analyses:

The following general statistical limitations should be considered when interpreting results of O/E and sensitivity analyses for all AESIs:

- For the overall O/E results, AE reports with unknown TTO were conservatively included in observed counts and the possibility that the numerator was artificially inflated due to inclusion of AEs falling outside the risk window cannot be ruled out.
- The sensitivity analyses assuming underreporting at rates of 50% and 75% may overestimate the number of unreported AEs, particularly in the setting of highly publicised media coverage of vaccine safety, provider reporting requirements and increased public awareness.
- The use of large, multi-centre studies, such as the vACCine COVID-19 monitoring readinESS Project (Willame 2023) study, or the US FDA Biologics Effectiveness and Safety (Moll 2023) Initiative, are preferred sources of background rate data (refer to Appendix 10). In certain situations where background rates for certain AESI are not available from such sources, it may be necessary to utilize scientific literature. Overall, the data and methods used to generate the expected background rates may not reflect the types of data and methods from observed case data. Therefore, the potential for biased O/E results based on differences in observed versus expected rates cannot be fully excluded.
- Since Germany no longer provides exposure data, assumptions have been made to determine the exposure for the period after Apr-2023. The calculation is described in Appendix 10. Therefore, the denominator may be underestimated or overestimated and can lead to skewed O/E results.

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. No ICSRs were retrieved for the following 13 AESIs, cumulatively: Acute Disseminated Encephalomyelitis, Foetal Growth Restriction, Gestational Diabetes, Kawasaki's Disease, Major Congenital Anomalies, Maternal Death, Microcephaly, Narcolepsy, Neonatal Death, Preterm Birth, Stillbirth, Sudden Death and Transverse Myelitis.

- Anaphylaxis (refer to Section 15.3.1)
- Autoimmune Hepatitis (refer to Section 15.3.2)
- Autoimmune Thyroiditis (refer to Section 15.3.3)
- Bell's Palsy (refer to Section 15.3.4)
- Cerebral Venous Sinus Thrombosis (refer to Section 15.3.5)
- Chronic Fatigue Syndrome (refer to Section 15.3.6)
- Encephalitis, Encephalomyelitis (refer to Section 15.3.7)
- Fibromyalgia (refer to Section 15.3.8)
- Generalised Convulsions (refer to Section 15.3.9)
- Guillain-Barré Syndrome (refer to Section 15.3.10)
- Haemorrhagic Stroke (refer to Section 15.3.11)
- Ischaemic Stroke (refer to Section 15.3.12)
- Multiple Sclerosis (refer to Section 15.3.13)
- Multisystem Inflammatory Syndrome in Children (refer to Section 15.3.14)
- Myasthenia Gravis (refer to Section 15.3.15)
- Myocardial Infarction (refer to Section 15.3.16)
- Myocarditis and Pericarditis (refer to Section 15.3.17)
- Optic Neuritis (refer to Section 15.3.18)
- Postural Orthostatic Tachycardia Syndrome (refer to Section 15.3.19)
- Pre-eclampsia (refer to Section 15.3.20)
- Rheumatoid Arthritis (refer to Section 15.3.21)
- Spontaneous Abortion (refer to Section 15.3.22)
- Thrombocytopenia (refer to Section 15.3.23)
- Thrombosis with Thrombocytopenia Syndrome (refer to Section 15.3.24)
- Vaccine Associated Enhanced Disease (refer to Section 15.3.25)
- Venous Thromboembolism (refer to Section 15.3.26)

15.3.1 Anaphylaxis

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

Anaphylaxis will remain a closely monitored AESI for further characterisation in the post-authorisation real-world setting through routine pharmacovigilance practices and within post-authorisation safety studies and across clinical development programs. The general methods of AESI analyses are presented below.

15.3.1.1 Results and Discussion

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

Twenty-six ICSRs were retrieved for the interval (24 initial and 2 follow-ups).

Cumulatively, 69 ICSRs were retrieved (59 females, 10 males; age range 17 – 75 years when reported, median age 40.5 years). The 69 cumulative ICSRs included 81 AEs coded to PTs of Anaphylactic reaction (n=42), Anaphylactoid reaction (n=24), Anaphylactic shock (n=7), Circulatory collapse (n=6), Shock (n=1), and Type I hypersensitivity (n=1). All 81 cumulative AEs were designated as serious, meeting IME criteria, of which 15 AEs additionally involved hospitalisation, 1 AE involved patient disability, 4 AEs were considered life-threatening, and 1 AE involved hospitalisation and was considered life threatening.

Results of O/E with sensitivity analysis are presented in Table 18. In addition, O/E was performed for cumulative AEs stratified by age and sex and is presented in Table 19. O/E was also performed for adjudicated cases and results are presented in Table 20. Of the 69 total ICSRs, (66 ICSRs (9 males, 57 females), are included in overall, sex, and age-specific crude (pre-adjudicated) O/E results with a risk window of 0 – 7 days for anaphylaxis.

15.3.1.2 Results of O/E Analysis

Multiple sets of 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 42).

Refer to Table 17 for stratification of AEs included in O/E analysis.

Table 17: Stratification of AEs Included in O/E Analysis for Anaphylaxis

Total ICSRs	n=69
Total AEs reported	n=81
Total AEs included in O/E analysis	n=69 *
Number of AEs with TTO reported	63
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	6

Table 17: Stratification of AEs Included in O/E Analysis for Anaphylaxis

Total ICSRs	n=69
Total AEs reported	n=81
AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 1 day	4
Risk window 0 – 2 days	4
Risk window 0 – 7 days	3
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 1 day	65
Risk window 0 – 2 days	65
Risk window 0 – 7 days	66

*Note that a few of the reports contained 2 or more AEs with the same onset date in the same individuals, hence were pooled into one report for the O/E analysis.

Risk window 0 – 1 day: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 day (n=65), the observed rate showed an increase when compared to the expected rate with a statistically significant rate ratio (RR) of 14.52 (95% CI: 11.21 – 18.51). When assessing by vaccinee dose number, there were increased and statistically significant O/E results for Dose 1 (n=9) with an RR of 8.58 (95% CI: 3.93 – 16.29), for Dose 2 (n=6) with an RR of 7.46 (95% CI: 2.73 – 16.23) and for Booster doses (n=19) with an RR of 7.23 (95% CI: 4.35 – 11.28).

Risk window 0 – 2 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=65), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 7.25 (95% CI: 5.59 – 9.24). When assessing by dose number, there were increased and statistically significant O/E results for Dose 1 (n=9) with an RR of 4.32 (95% CI: 1.98 – 8.19), for Dose 2 (n=6) with an RR of 3.71(95% CI: 1.36 – 8.09) and for Booster doses (n=19) with an RR of 3.61 (95% CI: 2.17 – 5.64).

Risk window 0 – 7 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=66), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 2.10 (95% CI: 1.63 – 2.67). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 18: 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
All Doses			
0 – 1 Day	14.52 (11.21 – 18.51) *	29.04 (22.41 – 37.01) *	58.08 (44.83 – 74.02) *
0 – 2 Days	7.25 (5.59 – 9.24) *	14.49 (11.19 – 18.47) *	28.98 (22.37 – 36.94) *
0 – 7 Days	2.10 (1.63 – 2.67) *	4.20 (3.25 – 5.35) *	8.41 (6.50 – 10.70) *
Dose 1			
0 – 1 Day	8.58 (3.93 – 16.29) *	17.17 (7.86 – 32.58) *	34.34 (15.72 – 65.17) *
0 – 2 Days	4.32 (1.98 – 8.19) *	8.63 (3.95 – 16.38) *	17.26 (7.90 – 32.76) *
0 – 7 Days	1.23 (0.56 – 2.33)	2.46 (1.12 – 4.66) *	4.91 (2.25 – 9.32) *
Dose 2			
0 – 1 Day	7.46 (2.73 – 16.23) *	14.91 (5.47 – 32.46) *	29.82 (10.94 – 64.92) *
0 – 2 Days	3.71 (1.36 – 8.09) *	7.43 (2.72 – 16.17) *	14.86 (5.45 – 32.34) *
0 – 7 Days	1.06 (0.39 – 2.31)	2.12 (0.78 – 4.62)	4.24 (1.56 – 9.24) *
Booster			
0 – 1 Day	7.23 (4.35 – 11.28) *	14.45 (8.70 – 22.57) *	28.90 (17.40 – 45.13) *
0 – 2 Days	3.61 (2.17 – 5.64) *	7.22 (4.35 – 11.27) *	14.44 (8.69 – 22.54) *
0 – 7 Days	1.03 (0.62 – 1.61)	2.06 (1.24 – 3.22) *	4.13 (2.49 – 6.45) *

* Increased and statistically significant O/E results.

15.3.1.2.1 Results of O/E Analysis stratified by Age and Sex

The results of O/E analysis accounting for a 7-day risk window, stratified by age and sex for anaphylaxis are presented in Table 19 below. When accounting for all cumulative anaphylaxis reports meeting inclusion criteria (n=66) stratified by age and sex; the crude observed rate as reported in the total male group (n=9) showed a statistically significant increase when compared to the expected rate with an RR of 5.99 (95% CI: 2.74 – 11.37). Statistically significant increases were seen in the 20 – 29-year-old male group (n=2) with an RR of 12.41 (95% CI: 1.49 – 44.78), in the 30 – 39-year-old male group (n=2) with an RR of 8.45 (95% CI: 1.01 – 30.51) and the 40 – 49-year-old male group (n=3) with an RR of 10.64 (95% CI: 2.20 – 31.10). A non-statistically significant increase was observed in the 50 – 59-year-old male group (n=1). The crude observed rate as reported in the total female group (n=57) showed an increase compared to the expected rate, and this increase was statistically significant with an RR of 14.61 (95% CI: 11.07 – 18.93). Results showed a statistically significant increase in the 0-19-year-old female group (n=4) with an RR of 52.65 (95% CI: 14.35 – 134.78), in the 20 – 29-year-old female group (n=4) with an RR of 9.56 (95% CI: 2.61 – 24.47), in the 30 – 39-year-old female group (n=15) with an RR of 18.22 (95% CI: 10.20 – 30.05), in the 40 – 49-year-old female group (n=20) with an RR of 21.23 (95% CI: 12.97 – 32.79), the 50 – 59-year-old female group (n=10) with an RR of 11.55 (95%

CI: 5.54 – 21.24), and in the 60 – 69-year-old female group (n=4) with an RR of 7.68 (95% CI: 2.09 – 19.65).

Table 19: O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Doses				
0 – 19	0	0 (0 – 31.97)	4	52.65 (14.35 – 134.78) *
20 – 29	2	12.41 (1.49 – 44.78) *	4	9.56 (2.61 – 24.47) *
30 – 39	2	8.45 (1.01 – 30.51) *	15	18.22 (10.20 – 30.05) *
40 – 49	3	10.64 (2.20 – 31.10) *	20	21.23 (12.97 – 32.79) *
50 – 59	1	3.40 (0.10 – 18.92)	10	11.55 (5.54 – 21.24) *
60 – 69	0	0 (0 – 13.34)	4	7.68 (2.09 – 19.65) *
70 – 79	0	0 (0 – 33.48)	0	0 (0 – 18.24)
80+	0	0 (0 – 142.18)	0	0 (0 – 71.88)
Missing	1	N/A	0	N/A
Total	9	5.99 (2.74 – 11.37) *	57	14.61 (11.07 – 18.93) *

* Increased and statistically significant O/E results.

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

A total of 69 cases retrieved by the narrow search strategy were adjudicated against the established Brighton Collaboration (BC) case definition for Anaphylaxis. Of the 69 ICSRs for anaphylaxis, 15 cases were adjudicated to BC Level 1 – 3 criteria. O/E analysis was generated for anaphylaxis for adjudicated cases using the following risk windows; 0 – 1 day, 0 – 2 days and 0 – 7 days (Refer to Table 42). A TTO of 0 was reported for all 15 adjudicated cases and therefore all cases (n=15) were included in the analysis for all risk windows.

Refer to Table 20 for O/E results following adjudication, for BC Level 1-3 anaphylaxis cases.

Table 20: O/E Analysis (BC Levels 1-3) following Adjudication – All Cumulative adjudicated AEs

Risk Window	O/E Rate Ratio (95 % CI)
All doses	
0 – 1 Day	3.35 (1.88 – 5.53) *
0 – 2 Days	1.67 (0.94 – 2.76)
0 – 7 Days	0.48 (0.27 – 0.79) **

Table 20: O/E Analysis (BC Levels 1-3) following Adjudication – All Cumulative adjudicated AEs

Risk Window	O/E Rate Ratio (95 % CI)
Dose 1	
0 – 1 Day	1.91 (0.23 – 6.89)
0 – 2 Days	0.96 (0.12 – 3.46)
0 – 7 Days	0.27 (0.03 – 0.99) **
Dose 2	
0 – 1 Day	2.49 (0.30 – 8.97)
0 – 2 Days	1.24 (0.15 – 4.47)
0 – 7 Days	0.35 (0.04 – 1.28)
Booster Dose	
0 – 1 Day	2.66 (1.07 – 5.48) *
0 – 2 Days	1.33 (0.53 – 2.74)
0 – 7 Days	0.38 (0.15 – 0.78) **

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

Risk window 0 – 1 day: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 day (n=15), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 3.35 (95% CI: 1.88 – 5.53). When assessing by dose number, there were increased and statistically significant O/E results for Booster dose (n=7) with an RR of 2.66 (95% CI: 1.07 – 5.48).

Risk window 0 – 2 days: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=15), the observed rate showed an increase when compared to the expected rate, but this increase was not statistically significant. When assessing by dose number, none of the results were both increased and statistically significant.

Risk window 0 – 7 days: When accounting for all cumulative adjudicated anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=15), none of the results were increased.

15.3.1.4 Limitations to O/E Analysis

In addition to the general statistical limitations presented in Section 15.3 the possibility of overestimation of the observed count for anaphylaxis overall O/E analysis must be considered, as 6 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator artificially.

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

Demographic information on age was only available in exposure data from Australia (until 21-Dec-2022), 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 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 current available exposure data do not provide age-/sex-specific information for stratified analysis, and the method currently used is not reliable.

15.3.1.6 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 Section 15.2.

15.3.1.7 Conclusion

A total of 81 AEs were reported cumulatively, most of which were coded to PT Anaphylactic reaction (n=42, 51.8%). The majority of the ICSRs involved females (n=59, 72.8%).

With the exclusion of 3 reports which fell outside the risk window for 0 – 7 days, 66 AEs met inclusion criteria for the crude observed count for O/E analyses for the 0 – 7 days risk window. The crude O/E results showed an increase in the observed rate compared to the expected rate which was statistically significant. O/E results also showed an increase in the observed rate for the 0 – 1 and 0 – 2 risk windows. Results for all reports stratified by age and sex were statistically significant for the total male group, males 20 – 49 years, females 0 – 69 years, and the total female group.

A total of 15 case reports met BC case Levels 1 – 3 for anaphylaxis and were included in the adjudicated analysis.

For this refined analysis of cases meeting BC Levels 1 – 3, the O/E results showed a statistically significant increase in the observed rate compared to the expected rate for the 0 – 1-day risk window. By vaccinee dose number, the only result that was increased and statistically significant was for the 0 – 1-day booster dose (n=7), likely influenced by low numbers overall.

Overall, results showed that when only adjudicated cases are considered, the O/E remains increased and statistically significant compared to unadjudicated results for a 0 – 1 day risk

window. Though it remained increased and statistically significant, there was a 76.9% reduction in adjudicated O/E results.

This AESI underwent complete signal evaluation and was confirmed as signal. Anaphylaxis was added to 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.

15.3.2 Autoimmune Hepatitis

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

15.3.2.1 Results and Discussion

No ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (female, age 44 years). The single cumulative ICSR included 1 AE coded to PT of Autoimmune hepatitis (n=1). This AE was designated as serious by convention, meeting IME criteria and involved hospitalisation. The MAH considers the causality for the event as indeterminate. There is an unlikely temporal association: the event occurred 92 days after the last dose of vaccine, beyond the 42 day-risk window established by Center for Biologics Evaluation and Research (CBER) and WHO. In addition, the current literature describes a latency of 3 – 54 days (Izagirre 2022) and 3 – 65 days (Efe 2022) for events of autoimmune hepatitis following COVID-19 vaccination. Insufficient information was provided for robust analysis of the event, including lack of medical confirmation, information about baseline medical history or diagnostic testing results.

Results of O/E analyses are presented below.

15.3.2.2 Results of the O/E Analysis

The TTO for this single AE was reported as 92 days and fell outside the risk window of 0 – 42 days (refer to Table 42). Hence, this single AE did not meet the inclusion criteria for the observed count for O/E analyses.

15.3.2.3 Conclusion

This single ICSR did not meet the TTO inclusion criteria for O/E analyses.

No safety signal was identified.

15.3.3 Autoimmune Thyroiditis

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

15.3.3.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 3 ICSRs were retrieved (3 females, age range 34 – 42 years when reported). The 3 cumulative ICSRs included 3 AEs coded to PTs of Thyroiditis (n=1), Autoimmune Thyroiditis (n=1) and Graves' disease (n=1). One of the AEs (thyroiditis) was non-serious, another AE (Graves' disease) was designated as serious by convention, meeting IME criteria and the remaining AE (autoimmune thyroiditis) was serious due to disability and meeting IME criteria.

Results of O/E analyses are presented below.

15.3.3.2 Results of the O/E Analysis

The TTO was not reported for any of the AEs, and they were conservatively assumed to fall within the risk window of 0 – 42 days (refer to Table 42). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.3.3 Conclusion

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

No safety signal was identified.

15.3.4 Bell's Palsy

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

15.3.4.1 Results and Discussion

Thirteen initial ICSRs were retrieved for the interval.

Cumulatively, 23 ICSRs were retrieved (13 females, 10 males, age range 20 – 77 years when reported, median age 47 years). The 23 cumulative ICSRs included 24 AEs coded to PTs of Facial paralysis (n=20), Bell's palsy (n=3) and Facial paresis (n=1). All 24 AEs were designated as serious: 23 AEs met IME criteria, with 4 of these AEs additionally involving hospitalisation; 1 AE (PT: Facial paresis) in a 30-year-old female met hospitalisation criteria only.

Results of O/E analyses are presented below.

15.3.4.2 Results of the O/E Analysis

The TTO for 21 of 24 AEs ranged from 0 – 23 days which are within the risk window of 0 – 42 days (refer to Table 42). TTO was not reported for the other 3 AEs and were conservatively included in the O/E analyses. Therefore, all AEs met inclusion criteria for the observed count (n=24). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.4.3 Conclusion

Cumulatively, 24 AEs were reported, most of which were coded to PT Facial paralysis (n=20, 83.3%).

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

No safety signal was identified.

15.3.5 Cerebral Venous Sinus Thrombosis

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

15.3.5.1 Results and Discussion

One initial ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (male, 67 years). This 1 cumulative ICSR included 1 serious AE coded to PT: cerebral venous sinus thrombosis, designated as serious by convention for 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 also was retrieved in the search results for Venous Thromboembolism (Section 15.3.26).

Results of O/E analyses are presented below.

15.3.5.2 Results of the 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 42) and met inclusion criteria for the observed count (n=1). Crude O/E analyses results showed that the observed rate was lower than the expected rate. When assuming

50% and 75% underreporting, there was an increase in the observed rate versus the expected rate, however this increase was not statistically significant.

15.3.5.3 Conclusion

The single ICSR met TTO inclusion criteria and O/E analysis showed the observed count was increased compared to expected count at 50% and 75% sensitivity, but this increase was not statistically significant.

No safety signal was identified.

15.3.6 Chronic Fatigue Syndrome

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

15.3.6.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 2 ICSRs were retrieved (1 female and 1 male, ages 44 and 32 years, respectively). The 2 cumulative ICSRs included 2 non-serious AEs coded to PT: Chronic fatigue syndrome.

Results of O/E analyses are presented below.

15.3.6.2 Results of the O/E Analysis

The TTO for one of the two AEs was reported as 1 day which is within risk window of 0 – 42 days (refer to Table 42). The TTO was not reported for the other AE and was conservatively included in the O/E analyses. Therefore, both AEs met the inclusion criteria for the observed count (n=2). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.6.3 Conclusion

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

No safety signal was identified.

15.3.7 Encephalitis and Encephalomyelitis

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

15.3.7.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 3 ICSRs were retrieved (2 females, 1 male; age range 42 – 67 years, median age 57 years). The 3 ICSRs included 3 AEs coded to PTs of Noninfective encephalitis (n=2) and Encephalitis (n=1). All 3 AEs were designated as serious by convention, meeting IME criteria, of which 1 AE (PT: Encephalitis) additionally involved hospitalisation.

Results of O/E with sensitivity analyses are presented below.

15.3.7.2 Results of the O/E Analysis

TTO for 2 of 3 AEs were reported as 1 day and 28 days, respectively, both of which fell within the risk window of 0 – 42 days (refer to Table 42). The TTO was not reported for the other AE and was conservatively included in the O/E analyses. Therefore, all AEs met the inclusion criteria for the observed count (n=3). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.7.3 Conclusions

A total of 3 AEs were reported cumulatively, of which, 2 AEs were coded to Noninfective encephalitis (66.7%). The majority of ICSRs involved females (n=2, 66.7%)

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

No safety signal was identified.

15.3.8 Fibromyalgia

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

15.3.8.1 Results and Discussion

One initial ICSR was retrieved for the interval.

Cumulatively, 2 ICSRs (1 female age 49 years, 1 male of unknown age) were retrieved. The 2 cumulative ICSRs included 2 non-serious AEs coded to PT Fibromyalgia. The reported verbatim for 1 ICSR (male, unknown age) was 'fibromyalgia worsened' which occurred 2 days after receiving the first dose.

Results of O/E analyses are presented below.

15.3.8.2 Results of the O/E Analysis

TTO for 1 of 2 AEs was reported as 2 days which fell within the risk window of 0 – 42 days (refer to Table 42). The TTO was not reported for the other AE and was conservatively included in the O/E analyses. Therefore, all AEs met the inclusion criteria for the observed count (n=2). O/E and sensitivity analyses results showed the observed rate was lower than the expected rate.

15.3.8.3 Conclusion

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

No safety signal was identified.

15.3.9 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).

15.3.9.1 Results and Discussion

Four ICSRs were retrieved for the interval (3 initial and 1 follow-up).

Cumulatively, 13 ICSRs were retrieved (10 females, 3 males, age range 17 – 76 years, median age 30 years). The 13 cumulative ICSRs included 14 AEs coded to PTs of 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). One of the AEs (PT: Febrile convulsion) was non-serious. The remaining 13 AEs were designated as serious by convention, meeting IME criteria, of which, 2 AEs (Seizure) additionally met hospitalisation criteria, 2 AEs (Postictal state and Generalised tonic-clonic seizure) met both hospitalisation and life-threatening criteria, and 1 AE (Seizure) had a fatal outcome.

Results of O/E analyses are presented below.

15.3.9.2 Results of the O/E Analysis

Multiple sets of O/E and sensitivity analyses were generated for generalised convulsions using the following risk windows: 0 – 1 day, 0 – 2 days, and 0 – 7 days (refer to Table 42). Two reports, one with two 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 analysis. The TTO was not reported for 2 AEs and conservatively included in the O/E analyses. The TTO was known for the other 9 of 14 AEs which fell within the 0 –7 day risk window and ranged from 0 – 6 days. Eleven AEs met the inclusion criteria for the observed count (n=11) 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=8), the observed rate was lower than the expected rate. When assuming 50% and 75% underreporting, there was an increase in the observed rate versus the expected rate, however this increase was not statistically significant.

Additional risk windows: When accounting for all cumulative generalised convulsions AEs meeting inclusion criteria, multiple O/E analyses calculated using risk windows of 0 – 7 days (n=11) and 0 – 2 days (n=9) each showed that the overall observed rate was lower than the expected rate.

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

15.3.9.3 Limitations of O/E Analysis

In addition to general statistical limitations presented in Section 15, regional background rates from Canada represent febrile convulsions only, a subset of generalized convulsions, therefore potentially leading to an underestimation of the expected cases and inflated O/E analysis.

15.3.9.4 Conclusion

Eleven AEs met inclusion criteria for O/E analyses for the 0 – 7-day risk window. O/E analysis showed that the overall observed rate was lower than the expected rate for risk windows 0 – 1, 0 – 2 and 0 – 7 days. O/E analysis calculated using risk window of 0 – 1 days showed the observed count was increased compared to expected count at 50% and 75% sensitivity, but this increase was not statistically significant.

No safety signal was identified.

15.3.10 Guillain-Barré Syndrome

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

15.3.10.1 Results and Discussion

Four initial ICSRs were retrieved for the interval.

Cumulatively, 7 ICSRs were retrieved (2 females, 5 males, age range 18 – 82 years, median age 55 years). The 7 cumulative ICSRs included 7 AEs coded to PT: Guillain-Barre syndrome (n=7). All 7 cumulative AEs were designated as serious by convention, meeting IME criteria, with 1 AE additionally involving hospitalisation.

Results of O/E analyses are presented below.

15.3.10.2 Results of the O/E Analysis

The TTO of 2 of 7 AEs were 57 days and 74 days respectively, which fell outside the risk window of 0 – 42 days (refer to Table 42) and therefore were not included in the O/E analysis. The TTO for the remaining 5 AEs ranged from 0 – 12 days and were included in the O/E analysis (n=5). The observed rate was lower than expected rate. However, when assuming 50% and 75% underreporting, results showed a non-statistically significant increase compared to the expected rate.

15.3.10.3 Conclusion

Five of 7 ICSRs met TTO inclusion criteria for O/E analyses, which showed the observed rate was increased compared to expected rate at 50% and 75% underreporting, but this increase was not statistically significant.

No safety signal was identified.

15.3.11 Haemorrhagic Stroke

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

15.3.11.1 Results and Discussion

Three initial ICSRs were retrieved for the interval.

Cumulatively, 10 ICSRs were retrieved (4 females, 6 males, age range 20 – 96 years, median age 60 years). The 10 cumulative ICSRs included 10 AEs coded to PT of Cerebrovascular accident (n=10). All AEs were designated as serious by convention, meeting IME criteria, of which 6 AEs additionally involved hospitalisation, 2 AEs involving patient death and 1 AE additionally met hospitalisation, life-threatening and disability criteria.

Of note, because the type of cerebrovascular accident was not indicated in the 10 ICSRs with PT Cerebrovascular accident, the same 10 ICSRs also were retrieved by the search strategy for ischaemic stroke (Section 15.3.12).

Results of O/E analyses are presented below.

15.3.11.2 Results of the O/E Analysis

The TTO for 4 out of 10 AEs ranged from 1 to 10 days which fell within the risk window of 0 – 28 days (refer to Table 42). TTO was not reported for 2 AEs and conservatively included in the O/E analysis. TTO for the remaining 4 AEs ranged from 31 days to 67 days, hence fell outside the risk window. Therefore, excluding 4 AEs falling outside the risk window, a total of

6 AEs met inclusion criteria for the observed count (n=6). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.11.3 Conclusion

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

No safety signal was identified.

15.3.12 Ischaemic Stroke

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

15.3.12.1 Results and Discussion

Five initial ICSRs were retrieved for the interval.

Cumulatively, 15 ICSRs were retrieved (7 females, 8 males, age range 20 – 96 years, median age 60 years). The 15 cumulative ICSRs included 15 AEs coded to PTs Cerebrovascular accident (n=10), Brain stem infarction (n=1) Carotid artery disease (n=1), Ischaemic stroke (n=1), Transient ischaemic attack (n=1) and Cerebral infarction (n=1). All 15 AEs were designated as serious by convention, meeting IME criteria, of which 8 AEs additionally involved hospitalisation, 2 AEs (PT: Cerebrovascular accident) additionally had fatal outcome, 1 AE (PT: Cerebral infarction) additionally met hospitalisation and disability criteria, 1 AE (PT: Transient ischaemic attack) met hospitalisation and life-threatening criteria and 1 AE (PT: cerebrovascular accident) met hospitalisation, life-threatening and disability criteria.

Of note, because the type of cerebrovascular accident was not indicated in the 10 ICSRs with PT Cerebrovascular accident, 10 of 15 ICSRs were retrieved by the search strategy for Haemorrhagic stroke (Section 15.3.11) as well.

Results of O/E analyses are presented below.

15.3.12.2 Results of the O/E Analysis

The TTO for 8 of 15 AEs ranged from 1 – 21 days which fell within the risk window of 0 – 28 days (refer to Table 42). TTO was not reported in 3 of the 15 AEs and these AEs were conservatively included in O/E analysis. TTO for the remaining 4 AEs ranged from 31 days to 67 days, hence fell outside the risk window. Therefore, excluding 4 AEs falling outside the risk window, 11 AEs met inclusion criteria for the observed count (n=11) for O/E analysis. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.12.3 Conclusion

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

No safety signal was identified.

15.3.13 Multiple Sclerosis

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

15.3.13.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 3 ICSRs were retrieved (2 females and 1 male, age range 36 – 63 years, median age 41 years). The 3 cumulative ICSRs included 3 AEs coded to PTs of Multiple sclerosis relapse (n=2) and Multiple sclerosis (n=1). All 3 cumulative AEs were designated as serious by convention, meeting IME criteria, of which 1 AE (PT: Multiple sclerosis) additionally met disability criteria.

Results of O/E analyses are presented below.

15.3.13.2 Results of the O/E Analysis

TTO of the 3 AEs ranged from 0 – 2 days which are within the risk window of 0 – 42 days (refer to Table 42). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.13.3 Conclusion

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

No safety signal was identified.

15.3.14 Multisystem Inflammatory Syndrome in Children

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

15.3.14.1 Results and Discussion

One initial ICSR was retrieved for the interval.

Cumulatively, no cases were retrieved involving children and 1 ICSR was retrieved for an adult (1 female, age 82 years). The single cumulative ICSR included 1 AE coded to PT of multisystem inflammatory syndrome (n=1) and was designated as serious by convention, meeting IME criteria, and additionally involved hospitalisation.

Results of O/E analysis are presented below.

15.3.14.2 Results of O/E Analysis

The TTO was reported as 8 days for this single report which fell within the risk window of 0 – 42 days (refer to Table 42). O/E and sensitivity analyses results showed the observed rate was lower than the expected rate.

15.3.14.3 Conclusion

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

No safety signal was identified.

15.3.15 Myasthenia Gravis

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

15.3.15.1 Results and Discussion

One initial ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (male, age 69 years). This single ICSR included 1 AE coded to PT Myasthenia Gravis, which was designated as serious by convention, meeting IME criteria, and additionally involved hospitalisation.

Results of O/E analyses are presented below.

15.3.15.2 Results of O/E Analysis

The TTO was reported as 23 days for this single report which fell within the risk window of 0 – 42 days (refer to Table 42). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.15.3 Conclusion

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

No safety signal was identified.

15.3.16 Myocardial Infarction

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

15.3.16.1 Results and Discussion

Two initial ICSRs were retrieved for the interval.

Cumulatively, 13 ICSRs were retrieved (5 females, 8 males, age range 24 – 93 years when reported, median age 50 years). The 13 cumulative ICSRs included 13 AEs coded to PTs Troponin increased (n=6), Acute myocardial infarction (n=3), Myocardial infarction (n=3), and Acute coronary syndrome (n=1). Ten out of 13 AEs were serious. Of these 10 AEs, 9 AEs were designated as serious by convention, meeting IME criteria, of which 5 AEs additionally involved hospitalisation and 1 AE (PT: Myocardial infarction) met hospitalisation and life-threatening criteria. One AE coded to PT: Troponin increased was serious due to hospitalisation only.

Results of O/E analyses are presented below.

15.3.16.2 Results of the O/E Analysis

The TTO for 6 of 13 AEs ranged from 0 – 14 days which fell within the risk window of 0 – 28 days (refer to Table 42). Three AEs with TTOs of 60 and 71 days, fell outside the risk window, hence, were excluded from the O/E analysis. TTO was not reported in the other 4 AEs which were conservatively included in the O/E analyses. Therefore 10 out of 13 AEs met TTO inclusion criteria for the observed count (n=10) for O/E analysis. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.16.3 Conclusion

Ten out of 13 AEs met TTO inclusion criteria and results of O/E analyses showed lower than expected rate.

No safety signal was identified.

15.3.17 Myocarditis and Pericarditis

A signal of myocarditis and pericarditis was validated on 17-May-2022 and signal evaluation was completed. On 03-Aug-2022, the signal of myocarditis and/or 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 will remain a closely monitored AESI for further characterisation in the post-authorisation real-world setting through routine pharmacovigilance practices and within post-authorisation safety studies and across clinical development programs.

15.3.17.1 Myocarditis

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

15.3.17.1.1 Results and Discussion

Nine ICSRs were retrieved for the interval (8 initial and 1 follow-up) using the narrow search strategy for myocarditis.

Cumulatively, 28 ICSRs were retrieved (14 females, 14 males, age range 18 – 83 years when reported, median age 32 years). The 28 cumulative ICSRs included 28 AEs coded to PTs Myocarditis (n=22) and Myopericarditis (n=6). All the 28 cumulative AEs were designated as serious by convention, meeting IME criteria, of which 8 AEs additionally involved hospitalisation.

Results of O/E with sensitivity analyses are presented below. In addition, O/E analysis was performed for cumulative AEs stratified by age and sex and results are presented in Table 23. Of the 28 total ICSRs, 26 ICSRs (13 males, 13 females), are included in overall, sex- and age-specific crude (pre-adjudicated) O/E results for myocarditis. Two ICSRs had AEs with a TTO that fell outside all risk windows and hence were excluded from the analysis.

15.3.17.1.2 Results of the O/E Analysis

Multiple sets of O/E and sensitivity analyses were generated for myocarditis using the following risk windows: 0 – 7 days, 0 – 14 days, 0 – 30 days, and 0 – 42 days (refer to Table 42). TTO was reported for 19 of the 28 AEs and was unknown for the remaining 9 AEs which were conservatively assessed as falling within the risk window. The TTO ranged from 0 – 21 days in 17 of the 19 AEs with known TTO. For the other two AEs with known TTO, they were reported as 102 days and 137 days respectively which fell outside all risk windows.

After excluding the AEs with TTOs of 102 days and 137 days, and additionally excluding 5 AEs with TTO ranging from 9 – 21 days, 21 of 28 AEs met TTO inclusion criteria for the observed count (n=21) within the risk window of 0 – 7 days.

After excluding the AEs with TTOs of 102 days and 137 days, and additionally excluding 3 AEs with TTO ranging from 16 – 21 days, 23 of 28 AEs met TTO inclusion criteria for the observed count (n=23) within the risk window of 0 – 14 days.

After excluding the AEs with TTOs of 102 days and 137 days, 26 of 28 AEs met TTO inclusion criteria for the observed count (n=26) withing the risk windows of 0 – 30 days and 0 – 42 days.

Refer to Table 21 for the stratification of AEs included in O/E analysis.

Table 21: Stratification of AEs Included In O/E Analysis for Myocarditis

Total ICSRs	n=28
Total AEs	n=28
Number of AEs with TTO reported	19
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	9
AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 7 days	7
Risk window 0 – 14 days	5
Risk window 0 – 30 days	2
Risk window 0 – 42 days	2
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	21
Risk window 0 – 14 days	23
Risk window 0 – 30 days	26
Risk window 0 – 42 days	26

Risk window 0 – 7 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=21), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 12.76 (95% CI: 7.90 – 19.50). When assessing by dose number for the vaccinee, results were increased and statistically significant for Dose 1 (n=3) with an RR of 7.07 (95% CI: 1.46 – 20.68) and for Dose 2 (n=4) with and RR of 12.51 (95% CI: 3.41 – 32.02).

Risk window 0 – 14 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=23), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 6.99 (95% CI: 4.43 – 10.49). When assessing by dose number for the vaccinee, results were increased and statistically significant for Dose 2 (n=4) with an RR of 6.25 (95% CI: 1.70 – 16.00).

Risk window 0 – 30 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=26), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 4.00 (95% CI: 2.61 – 5.86). When assessing by dose number, no O/E results were both increased and statistically significant.

Risk window 0 – 42 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=26), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 3.03 (95%

CI: 1.98 – 4.44). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 22: 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
All AEs			
0 – 7 Days	12.76 (7.90 – 19.50)*	25.52 (15.80 – 39.00)*	51.03 (31.59 – 78.01)*
0 – 14 Days	6.99 (4.43 – 10.49)*	13.98 (8.86 – 20.97)*	27.95 (17.72 – 41.94)*
0 – 30 Days	4.00 (2.61 – 5.86)*	8.00 (5.23 – 11.73)*	16.01 (10.45 – 23.45)*
0 – 42 Days	3.03 (1.98 – 4.44)*	6.06 (3.96 – 8.89)*	12.13 (7.92 – 17.77)*
Dose 1			
0 – 7 Days	7.07 (1.46 – 20.68)*	14.15 (2.92 – 41.36)*	28.29 (5.85 – 82.71)*
0 – 14 Days	3.54 (0.73 – 10.34)	7.07 (1.46 – 20.67)*	14.14 (2.92 – 41.34)*
0 – 30 Days	2.36 (0.49 – 6.89)	4.72 (0.97 – 13.79)	9.43 (1.95 – 27.58)*
0 – 42 Days	2.36 (0.49 – 6.89)	4.72 (0.97 – 13.79)	9.43 (1.95 – 27.58)*
Dose 2			
0 – 7 Days	12.51 (3.41 – 32.02)*	25.02 (6.82 – 64.04)*	50.03 (13.63 – 128.08)*
0 – 14 Days	6.25 (1.70 – 16.00)*	12.50 (3.41 – 31.99)*	24.99 (6.81 – 63.98)*
0 – 30 Days	2.92 (0.80 – 7.47)	5.84 (1.59 – 14.95)*	11.68 (3.18 – 29.89)*
0 – 42 Days	2.09 (0.57 – 5.34)	4.17 (1.14 – 10.69)*	8.35 (2.28 – 21.38)*
Booster			
0 – 7 Days	1.11 (0.03 – 6.17)	2.22 (0.07 – 12.35)	4.43 (0.13 – 24.70)
0 – 14 Days	0.55 (0.02 – 3.09)	1.11 (0.03 – 6.18)	2.22 (0.07 – 12.35)
0 – 30 Days	0.26 (<0.01 – 1.44)	0.52 (0.02 – 2.89)	1.04 (0.03 – 5.78)
0 – 42 Days	0.19 (<0.01 – 1.03)	0.37 (0.01 – 2.07)	0.74 (0.02 – 4.14)

* Increased and statistically significant O/E results

15.3.17.1.2.1 Results of O/E Analysis Stratified by Age and Sex

When accounting for all cumulative myocarditis AESI reports (n=26), stratified by age and sex with a risk window of 0 – 42 days, the crude observed rate as reported in the total male group (n=13) showed a statistically significant increase in the observed rate compared to the expected rate with an RR of 2.62 (95% CI: 1.40 – 4.48). Results were increased and statistically significant in the total female group (n=13) with an RR of 2.91 (95% CI: 1.55 – 4.98). This was also the case for the 0 – 19-year-old male group (n=3) with an RR of 34.76 (95% CI: 7.18 – 101.61) and in the 20 – 29-year-old female group (n=6) with an RR of 17.00 (95% CI: 6.23 – 37.00). In the 20 – 29-year-old male group (n=2), 30 – 39-year-old male group (n=3), 40 – 49-year-old male group (n=3), 50 – 59-year-old male group (n=1), the 80 years and older

male group, 30 – 39-year-old female group (n=1), 40 – 49-year-old female group (n=2), 50 – 59-year-old female group (n=1), and the 70 – 79-year-old female group (n=1), there was an increase in the observed rate versus the expected rate, but this increase was not statistically significant.

Table 23: O/E Analysis of Myocarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	**3**	**34.76 (7.18 – 101.61) ***	**0**	**0 (0 – 138.76)**
20 – 29	2	2.23 (0.27 – 8.06)	6	17.00 (6.23 – 37.00) *
30 – 39	3	2.49 (0.51 – 7.27)	1	1.20 (0.04 – 6.66)
40 – 49	3	2.99 (0.62 – 8.75)	2	2.27 (0.27 – 8.18)
50 – 59	1	1.49 (0.04 – 8.28)	2	2.17 (0.26 – 7.85)
60 – 69	0	0 (0 – 5.87)	0	0 (0 – 4.47)
70 – 79	0	0 (0 – 11.21)	1	2.30 (0.07 – 12.80)
80+	1	7.26 (0.22 – 40.46)	0	0 (0 – 19.62)
Missing	0	N/A	1	N/A
Total	13*	2.62 (1.40 – 4.48) *	13**	2.91 (1.55 – 4.98) *

* One AE with TTO of 102 days fell outside all risk windows
* *One AE with TTO of 137 days fell outside all risk windows
*** Increased and statistically significant O/E results.

15.3.17.1.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.3 , the possibility of overestimation of the observed count for myocarditis must be considered, as 9 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator artificially.

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

Demographic information on age and sex was only available in exposure data from Australia (until 21-Dec-2022), EU, Switzerland, Japan, UK and New Zealand, and none 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 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.

15.3.17.1.4 Conclusion

Cumulatively, there were 28 ICSRs received with a total of 28 AEs for the AESI of myocarditis, the majority of which were coded to PT Myocarditis (n=22, 78.6%). The male to female ratio of the 28 reports was equal, involving male individuals (n=14, 50%) and female individuals (n=14, 50%). The age range was 18 – 83 years with a median age of 32 years. The majority of reports involved individuals under the age of 50 years (within the age range of 18 – 47 years, n=22; 78.6%).

Result of O/E analysis showed a statistically significant increase in the observed rate compared to the expected rate when considering all reports of myocarditis. The increase in observed rate compared to expected rate was statistically significant for all risk windows.

Results of the 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 statistically significant increase in the 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.

15.3.17.2 Pericarditis

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

15.3.17.2.1 Results and Discussion

During the reporting interval, 8 initial ICSRs were retrieved using the narrow search strategy.

Cumulatively, 50 ICSRs were retrieved (25 females, 25 males; age range 23 – 83 years when reported, median age 39 years). The 50 cumulative ICSRs included 50 AEs coded to PT Pericarditis (n=50). All 50 cumulative AEs were designated as serious by convention, meeting IME criteria, of which 12 AEs additionally met hospitalisation criteria, and 2 AEs met hospitalisation and life-threatening criteria.

Results of O/E with sensitivity analyses are presented below. In addition, O/E was performed for cumulative reports stratified by age and sex and is presented in Table 26. All 50 ICSRs

(25 males, 25 females), are included in overall, sex and age-specific crude (pre-adjudicated) O/E results for pericarditis.

15.3.17.2.2 Results of the O/E Analysis

Multiple sets of 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 42 for risk windows).

For the report [redacted] pericarditis AE with TTO of 25 days appeared due to database's auto calculation from first dose. However, upon review of the narrative, it was 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.

TTO for 34 out of 50 AEs ranged from 0 – 42 days. The TTO was not reported in the other 16 AEs which were conservatively assessed as falling within the risk window.

After excluding 9 AEs with TTO ranging from 9 – 42 days, 41 out of 50 AEs met TTO inclusion criteria for the observed count (n=41) within the risk window of 0 – 7 days.

After excluding 3 AEs with TTO from 15 – 42 days, 47 out of 50 AEs met TTO inclusion criteria for the observed count (n=47) within the risk window of 0 – 14 days.

After excluding one AE with TTO of 42 days, 49 out of 50 AEs met TTO inclusion criteria for the observed count (n=49) within the risk window of 0 – 30 days.

All AEs met TTO inclusion criteria for the observed count (n=50) for O/E analysis within the risk window of 0 – 42 days.

Refer to Table 24 for stratification of AEs included in O/E analysis.

Table 24: Stratification of AEs Included In O/E Analysis for Pericarditis

Total ICSRs	n=50
Total AEs	n=50
Number of AEs with TTO reported	34
Number of AEs TTO missing (conservatively assessed as falling withing the risk window)	16
AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 7 days	9
Risk window 0 – 14 days	3
Risk window 0 – 30 days	1
Risk window 0 – 42 days	0

Table 24: Stratification of AEs Included In O/E Analysis for Pericarditis

Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	41
Risk window 0 – 14 days	47
Risk window 0 – 30 days	49
Risk window 0 – 42 days	50

Risk window 0 – 7 days: When accounting for all cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=41), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 4.01 (95% CI: 2.88 – 5.44). When assessing by dose number, no O/E results were both increased and statistically significant.

Risk window 0 – 14 days: When accounting for all cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=47), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 2.30 (95% CI: 1.69 – 3.06). When assessing by dose number, no O/E results were both increased and statistically significant.

Risk window 0 – 30 days: When accounting for all cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=49), the observed rate, showed an increase when compared to the expected rate, but the increase was not statistically significant. When assessing by dose number, no O/E results were increased.

Risk window 0 – 42 days: When accounting for all cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=50), the observed rate was lower than the expected rate. When assessing by dose number, no O/E results were increased.

Table 25: 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**
All AEs			
0 – 7 Days	4.01 (2.88 – 5.44) *	8.02 (5.76 – 10.88) *	16.04 (11.51 – 21.76) *
0 – 14 Days	2.30 (1.69 – 3.06) *	4.60 (3.38 – 6.12) *	9.20 (6.76 – 12.23) *
0 – 30 Days	1.20 (0.89 – 1.59)	2.40 (1.78– 3.17) *	4.80 (3.55 – 6.35) *
0 – 42 Days	0.92 (0.68 – 1.21)	1.84 (1.37 – 2.43) *	3.68 (2.73 – 4.85) *
Dose 1			
0 – 7 Days	1.32 (0.27 – 3.85)	2.64 (0.54 – 7.71)	5.27 (1.09 – 15.41) *
0 – 14 Days	0.66 (0.14 – 1.93)	1.32 (0.27 – 3.85)	2.64 (0.54 – 7.70)
0 – 30 Days	0.44 (0.09 – 1.28)	0.88 (0.18 – 2.57)	1.76 (0.36 – 5.14)
0 – 42 Days	0.44 (0.09 – 1.28)	0.88 (0.18 – 2.57)	1.76 (0.36 – 5.14)

Table 25: 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
Dose 2			
0 – 7 Days	0.56 (0.02 – 3.12)	1.12 (0.03 – 6.24)	2.24 (0.07 – 12.47)
0 – 14 Days	0.28 (<0.01 – 1.56)	0.56 (0.02 – 3.12)	1.12 (0.03 – 6.23)
0 – 30 Days	0.26 (0.03 – 0.94) **	0.52 (0.06 – 1.89)	1.05 (0.13 – 3.77)
0 – 42 Days	0.19 (0.02 – 0.67) **	0.37 (0.04 – 1.35)	0.75 (0.09 – 2.70)
Booster			
0 – 7 Days	0.65 (0.18 – 1.66)	1.30 (0.35 – 3.32)	2.60 (0.71 – 6.65)
0 – 14 Days	0.41 (0.13 – 0.95) **	0.81 (0.26 – 1.89)	1.62 (0.53 – 3.79)
0 – 30 Days	0.19 (0.06 – 0.44) **	0.38 (0.12 – 0.89) **	0.76 (0.25 – 1.77)
0 – 42 Days	0.14 (0.04 – 0.32) **	0.27 (0.09 – 0.63) **	0.54 (0.18 – 1.27)

***** Increased and statistically significant O/E result

15.3.17.2.2.1 Results of O/E Analysis Stratified by Age and Sex

When accounting for all cumulative Pericarditis AESI reports (n=50), stratified by age and sex, the crude observed rate as reported in the total male group (n=25) showed an increase when compared to the expected rate, but this increase was not statistically significant. Statistically significant increased results were observed in the 20 – 39-year-old male group (n=15) with an RR of 1.92 (95% CI: 1.07 – 3.16). In the total female group (n=25), the 20 – 39-year-old female group (n=11) and the 40 – 59-year-old female group (n=10), there was an increase in the observed rate versus the expected rate, but this increase was not statistically significant.

Table 26: O/E Analysis of Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	0	0 (0 – 23.29)	0	0 (0 – 23.66)
20 – 39	15	1.92 (1.07 – 3.16) *	11	1.83 (0.91 – 3.28)
40 – 59	8	0.75 (0.32 – 1.48)	10	1.09 (0.52 – 2.01)
60+	1	0.14 (<0.01 – 0.80) **	4	0.55 (0.15 – 1.40)
Missing	1	N/A	0	N/A
Total	25	1.02 (0.66 – 1.50)	25	1.05 (0.68 – 1.55)

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

15.3.17.2.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.3, the possibility of overestimation of the observed count for pericarditis must be considered, as 16 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator artificially.

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

Demographic information on age and sex was only available in exposure data from Australia (until 21-Dec-2023), 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.

15.3.17.2.4 Conclusion

Cumulatively, 50 ICSRs were received that reported 50 AEs coded to PT pericarditis. Half of the ICSRs involved males (n=25, 50.0%).

The O/E result showed an increased observed rate that was statistically significant for 0 – 7 and 0 – 14-day risk windows. The O/E result for all reports stratified by age and sex considering the 0 – 42 days risk window showed a statistically significant increase in the observed rate compared to the expected rate in the 20 – 39-year-old male group.

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

15.3.17.3 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).

15.3.17.3.1 Results and Discussion

During the reporting interval, 16 ICSRs were retrieved using the prespecified search strategy for myocarditis and pericarditis (15 initial and 1 follow-up).

Cumulatively, 79 ICSRs were retrieved (41 females, 38 males, age range 18 – 83 years when reported, median age 38.5 years). The 79 cumulative ICSRs included 80 AEs coded to PTs Pericarditis (n=50), Myocarditis (n=22), Myopericarditis (n=6), and Carditis (n=2). All 80 cumulative AEs were designated as serious by convention, meeting IME criteria, of which 20 AEs additionally met hospitalisation criteria, and 2 AEs met both hospitalisation and LT criteria.

Results of O/E with sensitivity analyses and O/E analysis stratified by age and sex are presented below. In addition, O/E was performed for cumulative AEs stratified by age and sex and are presented in Table 29. Of the 79 total ICSRs, 77 ICSRs (37 males, 40 females), are included in overall, sex and age-specific crude (pre-adjudicated) O/E results for myocarditis and pericarditis.

15.3.17.3.2 Results of the O/E Analysis

Multiple sets 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 42 for risk windows).

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

The TTO was reported for 53 out of the 79 AEs included in the O/E analysis and was unknown for the remaining 26 AEs which were conservatively assessed as falling within the risk window. The TTO ranged from 0 – 42 days in 51 out of 53 AEs with known TTO. In the other two AEs with known TTO, they were reported as 102 days and 137 days respectively, which fell outside all risk windows.

After excluding the AEs with TTO of 102 days and 137 days, and additionally excluding 14 AEs with TTO ranging from 9 – 42 days, 63 of 79 AEs met TTO inclusion criteria for the observed count (n=63) within the risk window of 0 – 7 days.

After excluding the AEs with TTOs of 102 days and 137 days, and additionally excluding 6 AEs with TTO ranging from 15 – 42 days, 71 of 79 AEs met TTO inclusion criteria for the observed count (n=71) within the risk window of 0 – 14 days.

After excluding the AEs with TTOs of 102 days and 137 days, and additionally excluding 1 AE with TTO of 42 days, 76 of 79 AEs met TTO inclusion criteria for the observed count (n=76) within the risk window of 0 – 30 days.

After excluding the AEs with TTOs of 102 days and 137 days, 77 of 79 AEs met TTO inclusion criteria for the observed count (n=77) for O/E analysis within risk window 0 – 42 days.

Refer to Table 27 for stratification of AEs included in O/E analysis.

Table 27: Stratification of AEs Included In O/E Analysis for Myocarditis and Pericarditis

Total ICSRs	n=79
Total AEs	n=80
Number of AEs with TTO reported	54
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	26
AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 7 days	16
Risk window 0 – 14 days	8
Risk window 0 – 30 days	3
Risk window 0 – 42 days	2
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	63
Risk window 0 – 14 days	71
Risk window 0 – 30 days	76
Risk window 0 – 42 days	77

Risk window 0 – 7 days: When accounting for all cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=63), the observed rate showed

an increase when compared to the expected rate with a statistically significant RR of 5.20 (95% CI: 3.99 – 6.65). When assessing by dose number, no O/E results were both increased and statistically significant.

Risk window 0 – 14 days: When accounting for all cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=71), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 2.93 (95% CI: 2.29 – 3.69). When assessing by dose number, no O/E results were both increased and statistically significant.

Risk window 0 – 30 days: When accounting for all cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=76), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 1.58 (95% CI: 1.24 – 1.97). When assessing by dose number, no O/E results were increased.

Risk window 0 – 42 days: When accounting for all cumulative myocarditis and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=77), the observed rate showed an increase when compared to the expected rate, but this increase was not statistically significant. When assessing by dose number, no O/E results were increased.

Table 28: 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
All AEs			
0 – 7 Days	5.20 (3.99 – 6.65) *	10.39 (7.99 – 13.30) *	20.79 (15.97 – 26.60) *
0 – 14 Days	2.93 (2.29 – 3.69) *	5.86 (4.58 – 7.39) *	11.72 (9.15 – 14.78) *
0 – 30 Days	1.58 (1.24 – 1.97) *	3.15 (2.48 – 3.95) *	6.30 (4.97 – 7.89) *
0 – 42 Days	1.20 (0.95 – 1.50)	2.41 (1.90 – 3.01) *	4.81 (3.80 – 6.01) *
Dose 1			
0 – 7 Days	2.12 (0.78 – 4.62)	4.24 (1.56 – 9.23) *	8.48 (3.11 – 18.47) *
0 – 14 Days	1.06 (0.39 – 2.31)	2.12 (0.78 – 4.61)	4.24 (1.55 – 9.23) *
0 – 30 Days	0.71 (0.26 – 1.54)	1.41 (0.52 – 3.08)	2.83 (1.04 – 6.16) *
0 – 42 Days	0.71 (0.26 – 1.54)	1.41 (0.52 – 3.08)	2.83 (1.04 – 6.16) *
Dose 2			
0 – 7 Days	2.29 (0.74 – 5.34)	4.58 (1.48 – 10.69) *	9.16 (2.97 – 21.38) *
0 – 14 Days	1.14 (0.37 – 2.67)	2.29 (0.74 – 5.34)	4.57 (1.48 – 10.68) *
0 – 30 Days	0.64 (0.24 – 1.40)	1.28 (0.47 – 2.79)	1.57 (0.94 – 5.58)
0 – 42 Days	0.46 (0.17 – 1.00)	0.92 (0.34 – 2.00)	1.83 (0.67 – 3.99)

Table 28: O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

Booster			
0 – 7 Days	0.56 (0.15 – 1.44)	1.13 (0.31 – 2.88)	2.25 (0.61 – 5.76)
0 – 14 Days	0.35 (0.11 – 0.82) **	0.70 (0.23 – 1.64)	1.41 (0.46 – 3.28)
0 – 30 Days	0.16 (0.05 – 0.38) **	0.33 (0.11 – 0.77) **	0.66 (0.21 – 1.54)
0 – 42 Days	0.12 (0.04 – 0.27) **	0.24 (0.08 – 0.55) **	0.47 (0.15 – 1.10)

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

15.3.17.3.2.1 Results of O/E Analysis Stratified by Age and Sex

When accounting for all cumulative myocarditis and pericarditis reports with a risk window of 0 – 42 days (n=77), stratified by age and sex, the crude as reported observed rate in the total male group (n=37), was increased compared with the expected rate, and this increase was statistically significant with an RR of 1.64 (95% CI: 1.16 – 2.26). Statistically significant increased results were also observed in the 0 – 19-year-old male group (n=3) with an RR of 10.22 (95% CI: 2.11 – 29.87) and in the 20 – 29-year-old male group (n=13) with an RR of 4.21 (95% CI: 2.24 – 7.20).The crude as reported observed rate in total female group (n=40), was increased when compared with the expected rate, and this increase was statistically significant with an RR of 1.83 (95% CI: 1.31 – 2.50). Statistically significant increased results were observed in the 20 – 29-year-old female group (n=11) with an RR of 7.53 (95% CI: 3.76 – 13.47), in the 30 – 39-year-old female group (n=8) with an RR of 2.47 (95% CI: 1.06 – 4.86), and in the 40 – 49-year-old female group (n=10) with an RR of 2.38 (95% CI: 1.14 – 4.37). The observed rate was increased when compared with the expected rate, but this increase was not statistically significant in the 30-39-year-old male group (n=7), the 40 – 49-year-old male group (n=8) and the 80-year-old and older male group (n=1).

Table 29: O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	**Male**		**Female**	
	Report Count	**O/E Rate Ratio (95% CI)**	**Report Count**	**O/E Rate Ratio (95% CI)**
All Reports				
0 – 19	3	10.22 (2.11 – 29.87) *	0	0 (0 – 46.66)
20 – 29	13	4.21 (2.24 – 7.20) *	11	7.53 (3.76 – 13.47) *
30 – 39	7	1.53 (0.61 – 3.15)	8	2.47 (1.06 – 4.86) *
40 – 49	8	2.03 (0.88 – 4.00)	10	2.38 (1.14 – 4.37) *
50 – 59	4	0.99 (0.27 – 2.53)	5	0.93 (0.30 – 2.18)
60 – 69	0	0 (0 – 0.99)	4	0.96 (0.26 – 2.46)
70 – 79	0	0 (0 – 1.80)	1	0.41 (0.01 – 2.28)

Table 29: O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Sex

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)	Report Count	O/E Rate Ratio (95% CI)
All Reports				
0 – 19	3	10.22 (2.11 – 29.87) *	0	0 (0 – 46.66)
20 – 29	13	4.21 (2.24 – 7.20) *	11	7.53 (3.76 – 13.47) *
80+	1	1.29 (0.04 – 7.16)	0	0 (0 – 4.33)
Missing	1	N/A	1	N/A
Total	37	1.64 (1.16 – 2.26) *	40	1.83 (1.31 – 2.50) *

* Increased and statistically significant O/E results.

15.3.17.3.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.3, the possibility of overestimation of the observed count for myocarditis and pericarditis must be considered, as 26 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator artificially.

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

Demographic information on age and sex was only available in exposure data from Australia (until 21-Dec-2022), 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.

15.3.17.3.4 Conclusion

Cumulatively, there were 79 ICSRs identified for the AESI of myocarditis and pericarditis with a total of 80 AEs. The most frequently reported PTs were Pericarditis (n=50, 62.5%) and Myocarditis (n=22, 27.5%). More than half of the ICSRs involved females (n=41, 51.9%). The

age range was 18 – 83 years, with a median age of 38.5 years. The majority of reports involved individuals under the age of 50 years, within the age range of 18 – 48 years (n=62, 78.5%).

The O/E result for cumulative myocarditis and pericarditis showed an increased observed rate that was statistically significant for 0 – 7, 0 – 14 and 0 – 30 days risk windows.

The O/E result for all reports stratified by age and sex revealed an increased observed rate that was statistically significant in the total male group, the 0 – 29-year-old male group, the total female group, and the 20 – 49-year-old group.

This AESI underwent complete signal evaluation and was updated to an important identified risk. The AESI of myocarditis and pericarditis has been 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.

15.3.18 Optic Neuritis

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

15.3.18.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (1 female, age 37 years. This single cumulative ICSR included one AE coded to PT Optic neuritis. This AE was designated as serious by convention, meeting IME criteria. No details were provided in the report, precluding meaningful analysis.

Results of O/E analyses are presented below.

15.3.18.2 Results of the O/E Analysis

The TTO for this single AE was reported as 10 days which fell within the risk window of 0 – 42 days (refer to Table 42). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.18.3 Conclusion

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

No safety signal was identified.

15.3.19 Postural Orthostatic Tachycardia Syndrome

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

15.3.19.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 2 ICSRs were retrieved (1 male, 1 female, ages 32 and 38 years, respectively). The 2 cumulative ICSRs included 2 AEs coded to PT of postural orthostatic tachycardia syndrome (n=2). One of the 2 AEs was designated as serious by convention, meeting IME criteria; and the other AE was non-serious.

Results of O/E analyses are presented below.

15.3.19.2 Results of the O/E Analysis

TTO for 1 out of 2 AEs was reported as 4 days which fell within the risk window of 0 – 42 days (refer to Table 42). TTO was not reported for the other AE and was conservatively assumed to fall within the risk window of 0 – 42 days. Therefore, all AEs met the inclusion criteria for the observed count (n=2). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

Note that background rates for postural orthostatic tachycardia syndrome were captured from a study done in Finland (Skufca 2017). The study population consisted of adolescent girls and was identified utilising the Finnish Population Registry from 2002 – 2012. Cases in the study were identified using International Classification of Diseases (ICD) -10 codes pulled from the National Hospital Discharge Register. The rarity of diagnosis of postural orthostatic tachycardia syndrome leads to difficulty in finding a reliable background rate. This was the only study identified that used a large registry-based data source providing a population with data that is relatively current.

15.3.19.3 Conclusion

Two ICSRs met inclusion criteria for observed count and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.3.20 Pre-eclampsia

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

15.3.20.1 Results and Discussion

One follow-up ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (female, age 38 years). This ICSR included 1 AE coded to PT Pre-eclampsia and was designated as serious, meeting IME criteria.

15.3.20.2 Results of O/E Analysis

O/E analysis was not performed for Pre-eclampsia due to inability to accurately determine exposure in pregnant females alone and indeterminate risk windows.

15.3.20.3 Conclusion

No safety signal was identified.

15.3.21 Rheumatoid Arthritis

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

15.3.21.1 Results and Discussion

Three initial ICSRs were retrieved for the interval.

Cumulatively, 6 ICSRs were retrieved (3 females, 3 males, age range 29 – 74 years when reported, median age 49 years). The 6 cumulative ICSRs included 6 AEs coded to PTs: Rheumatoid arthritis (n=4), Polyarthritis (n=1) and Rheumatoid lung (n=1). One out of 6 AEs (coded to PT of Rheumatoid lung) was serious due to hospitalisation and fatal outcome. The remaining 5 AEs were designated as serious by convention, meeting IME criteria, of which 1 AE (PT: Polyarthritis) additionally involved hospitalisation.

Results of O/E analyses are presented below.

15.3.21.2 Results of the O/E Analysis

The TTO for 2 of 6 AEs was 0 and 3 days respectively which fell within the risk window of 0 – 42 days (refer to Table 42). The TTO was not reported for 1 AE which was conservatively included in O/E analyses. TTO for one AE was reported as -24 and was not included in O/E analysis. TTO of the remaining two AEs were reported as 131 days and 93 days, which fell outside the risk window of 0 – 42 days. Therefore, 3 out of 6 AEs met the inclusion criteria for the observed count (n=3). The O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.21.3 Conclusion

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

No safety signal was identified.

15.3.22 Spontaneous Abortion

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

15.3.22.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 4 ICSRs were retrieved (4 females, age range 23 – 31 years when reported). The 4 cumulative ICSRs included 4 AEs coded to PT Abortion spontaneous. All AEs were designated as serious by convention, meeting IME criteria.

No O/E analysis could be performed for spontaneous abortion, as the exposure is unknown in women of childbearing age.

15.3.22.2 Conclusion

No safety signal was identified.

15.3.23 Thrombocytopenia

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

15.3.23.1 Results and Discussion

Two initial ICSRs were retrieved for the interval.

Cumulatively, 7 ICSRs were retrieved (6 females, 1 male, age range 23 – 69 years, median age 36 years). The 7 cumulative ICSRs included 8 AEs coded to PTs Thrombocytopenia (n=5), Immune thrombocytopenia (n=2) and Thrombosis with thrombocytopenia syndrome (n=1). All 8 AEs were designated as serious by convention, meeting IME criteria, of which 3 AEs additionally involved hospitalisation, and 1 AE met other serious criteria.

Results of O/E analyses are presented below.

15.3.23.2 Results of the O/E Analysis

The TTO for 5 of 8 AEs ranged from 6 – 34 days which are within the risk window of 0 – 42 days (refer to Table 42). TTO was not reported in the other 3 AEs and were included in O/E analyses. Additionally, one of the reports contained two AEs coded to PTs Immune thrombocytopenia and Thrombocytopenia which reportedly occurred on the same day and hence were pooled into one report for the O/E analysis. Therefore, after pooling 2 AEs into one case, 7 AEs met inclusion criteria for the observed count (n=7) for O/E analysis. The O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.23.3 Conclusion

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

No safety signal was identified.

15.3.24 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).

15.3.24.1 Results and Discussion

One initial ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (male, 69 years) and included 1 AE coded to PT of Thrombosis with thrombocytopenia syndrome (n=1) which was designated as serious by convention, meeting IME criteria and hospitalisation.

Results of O/E analyses are presented below.

15.3.24.2 Results of O/E Analysis

TTO for this single report was 6 days which fell within the risk window of 0 – 28 days (refer to Table 42). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.24.3 Conclusion

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

No safety signal was identified.

15.3.25 Vaccine Associated Enhanced Disease

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

15.3.25.1 Results and Discussion

Six initial ICSRs were retrieved for the interval.

Cumulatively, 6 ICSRs were retrieved (6 males, age range 33 – 71 years, median age 55 years). The 6 cumulative ICSRs included 6 AEs coded to PTs Antibody-dependent enhancement (n=6). All 6 AEs were designated as serious by convention, meeting IME criteria.

15.3.25.2 Results of O/E Analysis

O/E analyses was not performed for Vaccine Associated Enhanced Disease, as it is not possible to determine expected rate for this AE, given that vaccine exposure is necessary to develop the condition.

15.3.25.3 Conclusion

No safety signal was identified.

15.3.26 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).

15.3.26.1 Results and Discussion

Six ICSRs were retrieved for the interval (4 initial and 2 follow-up).

Cumulatively, 22 ICSRs were retrieved (13 females, 9 males, age range 29 - 85 years when reported, median age 50 years). The 22 cumulative ICSRs included 25 AEs coded to PTs Pulmonary embolism (n=12), Thrombophlebitis (n=4), Deep vein thrombosis (n=3), Venous thrombosis (n=3), Superficial vein thrombosis (n=2), and Cerebral venous sinus thrombosis (n=1). Of the 25 AEs, 5 AEs were non-serious, and 20 AEs were serious. Eighteen of the 20 serious AEs were designated as serious by convention, meeting IME criteria, of which 8 AEs additionally involved hospitalisation and 4 AEs additionally met hospitalisation and life-threatening criteria. One AE (PT: Venous thrombosis) met hospitalisation criteria only, and 1 AE (PT Superficial vein thrombosis) met life-threatening and disability criteria.

Results of O/E analyses are presented below.

15.3.26.2 Results of the O/E Analysis

The O/E analysis was performed for the risk window of 0 – 28 days (refer to Table 42). The TTO for 20 of the 25 AEs ranged from 1 – 28 days and the TTO for the other 5 AEs was 34, 54, 61, 88 and 113 days respectively, hence fell outside the risk window. Two of the reports contained 2 AEs with the same TTO, hence were pooled into one report for the O/E analyses. Therefore, after pooling 2 AEs into one case for two reports and excluding 5 AEs falling outside the risk window, 18 AEs met the inclusion criteria for the observed count (n=18) for O/E analyses. The O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.3.26.3 Conclusion

Eighteen AEs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.4 Additional Safety Topics for Monitoring

The global vaccine safety database was queried for the cumulative period up to 19-Jun-2023 according to the prespecified search strategies for the safety topics listed below (refer to Appendix 13 for search strategy of safety topics).

- Death, All Cause (refer to Section 15.4.1)
- Cholecystitis (refer to Section 15.4.2)
- Diarrhoea (refer to Section15.4.3)
- Herpes Zoster (refer to Section 15.4.4)
- Inflammatory eye disorders (refer to Section 15.4.5)
- Menstrual disorders (refer to Section 15.4.6)
- Paraesthesia (refer to Section 15.4.7)
- Reactogenicity profile- second dose and boosters (based on impurity levels) (refer to Section 15.4.8)
- Review of safety concerns in elderly and off-label paediatric use (refer to Section 15.4.9)
- Vaccine anxiety-related reactions (refer to Section 15.4.10)
- Vaccination failures / lack of efficacy (refer to Section 15.4.11)

15.4.1 Death, All Cause

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

15.4.1.1 Results and Discussion

Nineteen initial ICSRs (16 ICSRs from South Korea) were retrieved for the interval.

Note: On two separate dates during the current reporting interval (03-Jan-2023 and 02-May-2023), NVX received a legacy, 6month bolus of AE data up to 16-Jun-2022 and 31-Dec-2022, respectively from South Korea (via Korea Institute of Drug Safety and Risk Management) through partner SK Bio. These ICSRs were entered into the NVX global safety database before the DLP of this PBRER.

Cumulatively, 28 ICSRs were retrieved (13 females, 15 males, age range 13 – 96 years when reported, median age 74.5 years). The 28 cumulative ICSRs included 49 fatal AEs and the most frequently reported PTs (n>1) with fatal outcome were Death (n=11), dyspnoea (n=4), pyrexia (n=3), headache (n=2), dizziness (n=2), Adverse event following immunization (n=2) and Cerebrovascular accident (n=2).

Appendix 19 includes a cumulative line listing of fatal cases received as of the DLP (19-Jun-2023).

Results of O/E analyses are presented below.

15.4.1.2 Results of O/E Analysis

The TTO in 23 of 28 reports with fatal outcome ranged from 0 – 60 days which fell within the risk window of 0 – 60 days (refer to Table 42). Two reports with fatal outcome had TTO of 85 days and 93 days, respectively, which fell outside the risk window and were excluded from the O/E. TTO was not reported for the other 3 reports, and these were conservatively included as falling within the risk window. Therefore, 26 of 28 reports met inclusion criteria for O/E (n=26) and the results showed that the observed count was lower than the expected count.

15.4.1.3 Conclusion

Twenty-six of 28 ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.4.2 Cholecystitis

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

No ICSRs were retrieved during the reporting interval.

Cumulatively, 8 ICSRs were retrieved (5 females, 3 males, age range 38 – 84 years when reported, median age 44 years). The 8 cumulative ICSRs included 8 AEs coded to PTs Abnormal faeces (n=3), Jaundice (n=2), Blood bilirubin increased (n=1), Faeces pale (n=1) and Gallbladder disorder (n=1). Of the 8 AEs, majority were non-serious (n=5, 63%); 3 AEs were designated serious of which 1 AE met IME criteria, 1 AE met IME criteria and involved hospitalisation and 1 AE involved hospitalisation only.

No change in the characteristics of this event has been identified following cumulative review. Cholecystitis will continue to be monitored through routine pharmacovigilance activities.

No safety signal was identified.

15.4.3 Diarrhoea

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

Forty-five ICSRs were retrieved for the interval (40 initial and 5 follow-ups). Of the 40 initial ICSRs, 30 ICSRs were reported from South Korea.

Note: On two separate dates during the current reporting interval (03-Jan-2023 and 02-May-2023), NVX received a legacy, 6-month bolus of AE data up to 16-Jun-2022 and 31-Dec-2022 respectively from South Korea (via Korea Institute of Drug Safety and Risk Management) through partner SK Bio. These ICSRs were entered into the NVX global safety database before the DLP of this PBRER.

Cumulatively, 132 ICSRs were retrieved (107 females, 25 males, age range 18 – 86 years when reported, median age 43.5 years). The 132 cumulative ICSRs included 133 AEs coded to PT diarrhoea. Of the 133 AEs, the majority were non-serious (n=112, 84.2%); 21 AEs were designated as serious, of which 9 AEs met IME criteria, 1 AE met IME criteria and disability, 10 AEs involved hospitalisation only and 1 AE met disability criteria only.

No safety signal was identified.

15.4.4 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).

Four initial ICSRs were retrieved during the reporting interval.

Cumulatively, 40 ICSRs were retrieved (11 males, 28 females, 1 individual of unspecified sex, age range 24 – 76 years when reported, median age 53 years). The 40 cumulative ICSRs included 42 AEs (5 serious and 37 non-serious) 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 5 serious AEs, 2 AEs met IME criteria, 1 AE met IME criteria and hospitalisation, 1 AE met IME criteria, hospitalisation and life-threatening and 1 AE involved hospitalisation only.

15.4.4.1 Results of the O/E Analysis

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 count was lower than the expected count for all risk windows. Refer to Appendix 11 for complete O/E results.

15.4.4.2 Conclusion

No safety signal was identified.

15.4.5 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).

Seven ICSRs were retrieved for the interval (4 initial and 3 follow-ups).

Cumulatively, 61 ICSRs were retrieved (49 females, 12 males, age range 16 – 72 years when reported, median age 46 years). The 61 cumulative ICSRs included 69 AEs (11 serious and 58 non-serious) coded to PTs Eye swelling (n=17), Photophobia (n=9), Ocular hyperemia (n=8), Diplopia (n=6), Swelling of eyelid (n=5), Eye inflammation (n=5), Lacrimation increased (n=5), Eye irritation (n=4), Eye pruritus (n=3), Eye discharge(n=2), Eyelid oedema (n=2), Idiopathic orbital inflammation (n=1), Iridocyclitis (n=1), and Uveitis (n=1). Of the 11 serious AEs, 7 AEs met IME criteria, 2 AEs involved hospitalisation only, 1 AE was life-threatening with hospitalisation and 1 AE involved disability and hospitalisation.

No safety signal was identified.

15.4.6 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 PV 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).

Thirty-two ICSRs were retrieved for the interval (26 initial and 6 follow-ups).

Cumulatively, 130 ICSRs were retrieved (130 females, age range 20 – 73 years when reported). The 130 cumulative ICSRs included 198 AEs (10 serious and 188 non-serious). The most frequently reported AEs (n>10) were coded to PTs Menstrual disorder (n=49), Heavy menstrual bleeding (n=39), Dysmenorrhoea (n=18), Abnormal uterine bleeding (n=18), Menstruation irregular (n=17), Amenorrhoea (n=15), Polymenorrhoea (n=12) and Intermenstrual bleeding (n=11). Of the 10 serious AEs, 8 AEs met IME criteria, and 2 AEs involved hospitalisation only.

No safety signal was identified.

15.4.6.1 Results of Menstrual Disorders Rechallenge

During this reporting interval, there were no new positive rechallenge cases.

15.4.7 Paraesthesia

The safety topic of paraesthesia was designated as a validated signal on 27-May-2022. As of 27-Jun-2022, this signal has been designated as confirmed and the CCDS has been updated to include paraesthesia following administration of NVX-CoV2373 in Section 4.8.

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

Forty-one ICSRs were retrieved for the interval (30 initial and 11 follow-ups).

Cumulatively, 382 ICSRs were retrieved (276 females, 105 males, 1 individual of unspecified sex, age range 13 – 81 years when reported). The 382 cumulative ICSRs included 476 AEs coded to PTs Paraesthesia (n=295), Hypoaesthesia (n=127), Burning sensation (n=35), Hyperaesthesia (n=9), Dysaesthesia (n=8), and Hemiparaesthesia (n=2). Of the 476 AEs, 64 AEs were designated as serious, of which 37 AEs met IME criteria, 23 AEs involved hospitalisation only, and 4 AEs involved disability.

No safety signal was identified.

15.4.8 Reactogenicity Profile-Second Dose and Boosters (Based on Impurity Levels)

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for reactogenicity profile-second dose and boosters (based on impurity levels) (refer to Appendix 13).

Twenty-eight ICSRs were retrieved for the interval (23 initial and 5 follow-ups).

Cumulatively, 130 ICSRs were retrieved for second dose and boosters, 128 of which contained batch numbers (39 males, 91 females, age range 17 – 93 years when reported). The 130 cumulative ICSRs included 925 AEs (64 serious and 764 non-serious). The most frequently reported AEs (n>20) were coded to PTs Headache (n=57), Fatigue (n=54), Pyrexia (n=37),

Malaise (n=34), Injection site pain (n=30), Chills (n=27), Nausea (n=25), Arthralgia (n=25), Myalgia (n=23) and Pain in extremity (n=21). The reports were reviewed to identify any trend related to adverse events reported with specific batches and 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.

15.4.9 Review of Safety Concerns in Elderly and Off-label Pediatric Use

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategies for review of safety concerns in elderly and off-label pediatric use (refer to Appendix 13).

15.4.9.1 Review of Safety Concerns in Elderly

Three-hundred eighty-four ICSRs were retrieved for the interval (378 initial and 6 follow-ups). Two hundred ninety-eight ICSRs reporting 650 AEs are from South Korea (92 serious [including 17 fatal AEs] and 558 non-serious AEs).

Cumulatively, 650 ICSRs were retrieved (422 females, 221 males, 7 individuals of unknown sex, age range 65 – 96 years when reported). These 650 ICSRs included 1,846 AEs. The most frequently reported AEs (n>30) were coded to PTs Myalgia (n=121), Headache (n=105), Dizziness (n=81), Hypersensitivity (n=80), Injection site pain (n=54), Pyrexia (n=54), Nausea (n=51), Fatigue (n=49), Dyspnoea (n=42), Chills (n=37), Rash (n=37), Pruritus (n=36), Chest pain (n=35), Arthralgia (n=35), Urticaria (n=32) and COVID-19 immunisation (n=31). Of the 1,845 AEs, 344 AEs were serious (including 38 fatal AEs) and 1,501 were non-serious AEs. The most frequently reported fatal AEs (n>1) were coded to PTs Death (n=10), Dyspnoea (n=4), Pyrexia (n=3), Cerebrovascular accident (n=2), Dizziness (n=2) and Headache (n=2).

No safety signal was identified.

15.4.9.2 Off-label Pediatric Use (less than 12 years)

Seven initial ICSRs were retrieved for the interval.

Cumulatively, 11 ICSRs were retrieved (4 females, 1 male, 6 individuals of unspecified sex, age range from 4 – 9 years for 8 ICSRs when reported, 2 neonates and 1 infant of unspecified age) which contained 18 non-serious AEs.

The PTs are presented in Table 30.

Table 30: AEs Reported for Off-Label Paediatric Use

MedDRA PT Age Groups	Interval			Cumulative		
	Fatal	Serious	Non-Serious	Fatal	Serious	Non-Serious
Child						
Vaccination error	0	0	0	0	0	2
Off label use	0	0	0	0	0	1
Wrong product administered	0	0	0	0	0	1
Product administered to patient of inappropriate age	0	0	4	0	0	5
No adverse event	0	0	4	0	0	4
Infant						
Influenza like illness	0	0	0	0	0	1
Neonate						
Suspected COVID-19	0	0	1	0	0	1
Low birth weight baby	0	0	1	0	0	1
Foetal exposure during pregnancy	0	0	2	0	0	2
Total	0	0	12	0	0	18

A review of these reports did not suggest any trends in AEs particular to this population compared to the AE profile as defined in the CCDS for the overall population.

No safety signal was identified.

15.4.10 Vaccine Anxiety-Related Reactions

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

Five ICSRs were retrieved for the interval (4 initial and 1 follow-up).

Cumulatively, 52 ICSRs were retrieved (43 females, 7 males, 2 individuals of unspecified sex, age range 19 – 65 years when reported). The 52 cumulative ICSRs included 52 AEs (6 serious and 46 non-serious) coded to PTs Anxiety (n=40), Nervousness (n=6), Agitation (n=4), Stress (n=1), and Tension (n=1). Of the 6 serious AEs, 3 AEs involved hospitalisation, 2 AEs met IME criteria, and 1 AE involved disability.

No safety signal was identified.

15.4.11 Vaccination Failures / Lack of Efficacy

Vaccination failure/lack of efficacy is a safety topic under surveillance to monitor efficacy of the vaccine in post-marketing setting.

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.

15.4.11.1 Results and Discussion

Seven ICSRs were retrieved for the interval (4 initial and 3 follow-ups).

Cumulatively, 12 ICSRs were retrieved (9 females, 3 males, age range 20 – 74 years when reported). The 12 cumulative ICSRs included 12 AEs coded to PTs Vaccination failure (n=11) and Paradoxical drug reaction (n=1). Of the 12 AEs, 9 AEs were designated as serious due to IME criteria, 1 AE met IME criteria and involved hospitalisation and disability criteria and 2 AEs were non-serious.

15.4.11.2 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 are provided in Table 31, reflective of EU Risk Management Plan (RMP) V 2.1, dated 01-Sep-2022. During the reporting period, the EU RMP has been updated to V 3.1, dated 06-Feb-2023 with no changes to the list of safety concerns mentioned below.

Table 31: 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

Supplementary information was reviewed for menstrual disorder (rechallenge) following the receipt of PRAC assessment of SSR 10 (8th SSR to EMA, first bi-monthly SSR). This review did not change the original assessment of refutation and the signal was closed during the reporting interval.

Additionally, supplementary information was reviewed for the previously evaluated signals of diarrhoea, dyspnoea and tinnitus following the receipt of PRAC assessment of the second bi-monthly SSR which did not change the original assessment, and the signals of diarrhoea and dyspnoea remained refuted, and the signal of tinnitus remained confirmed. All three signals were closed after the DLP.

The signal of sensorineural hearing loss was validated during the reporting interval following a health authority request (TGA) received on 15-Jun-2023 for safety assessment of this topic. The signal was refuted and closed following assessment, shortly after the DLP of this report (on 30-Jul-2023).

In addition, retrospective Level 2B (L2B) case information was downloaded from EudraVigilance for the previously validated signals of anaphylaxis, myocarditis/pericarditis,

paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus and non-validated signals of angina pectoris, hypertension, herpes zoster and oral herpes.

An updated Signal Evaluation Report (SER) was generated after the DLP, for the signal of Myocarditis and Pericarditis following an EMA Inspection finding related to the date of validation of the signal.

A summary of the results of evaluations of validated/non-validated signals that were evaluated/re-evaluated and closed (rejected/refuted or considered to be potential or identified risks following evaluation) during the reporting interval is presented below.

16.2.1 Menstrual Disorders Rechallenge

Additional analyses on the previously refuted safety signal of menstrual disorders in association with the administration of Nuvaxovid was performed in response to the request received on 28-Dec-2022 from PRAC pursuant to EMA PRAC assessment of SSR 10 (8th SSR to EMA, first bi-monthly SSR) (period covering 01-Sep-2022 to 15-Nov-2022) and the addendum SER was presented in Appendix 20.

The global vaccine safety database was queried using the Menstrual Disorders search strategy high level group term (HLGT): Menstrual cycle and uterine bleeding disorders, MedDRA version 25.1, for date range cumulative until 31-Dec-2022. ICSR field "Re-challenge" and narratives were reviewed for rechallenge information.

16.2.1.1 Results and Discussion

Cumulatively, 106 ICSRs were retrieved. There was 1 non-medically confirmed ICSR with positive rechallenge for NVX COVID-19 vaccine and 1 non-medically confirmed ICSR with negative rechallenge. Rechallenge information was not reported for the remaining 104 ICSRs.

16.2.1.2 Conclusion

There is limited data available to determine re-challenge information on menstrual disorders with the use of Nuvaxovid. The causal association between Nuvaxovid and menstrual disorders remains not supported. The sponsor will include discussion of new positive rechallenge cases in future SSRs and reassess causality based on new and cumulative information as warranted (See Section 15.4.6)

16.2.2 Diarrhoea

A signal of diarrhoea was validated on 14-Nov-2022, pursuant to PRAC's request in their assessment of PBRER V 1.0 (20-Dec-2021 to 19-Jun-2022). A complete signal evaluation was performed, and the SER was presented in bi-monthly SSR No.02 and PBRER No.02.

In response to the PRAC assessment comment from the review of second bi-monthly SSR and PBRER No.02, the original search strategy had been expanded for review. The HLT Diarrhoea (excl infective) was run across the safety database up to the DLP of the original SER (16-Nov-2022) and the resulting data was reviewed.

16.2.2.1 Results and Discussion

No new cases were identified by the expanded search strategy; therefore, this review did not change the signal assessment of Diarrhea from refuted. The addendum SER is presented in Appendix 21.

16.2.2.2 Conclusion

Diarrhoea remains a refuted signal that will continue to be monitored according to the NUVAXOVID surveillance plan.

16.2.3 Dyspnoea

A signal of dyspnoea was validated on 14-Nov-2022, pursuant to PRAC's request in their assessment of PBRER V 1.0 (20-Dec-2021 to 19-Jun-2022). A complete signal evaluation was performed, and the SER was presented in bi-monthly SSR No.02 and PBRER No.02.

Supplementary information was reviewed for the previously refuted signal of dyspnoea following the receipt of the PRAC assessment report of the second bi-monthly SSR. Review included expanded search strategy for additional PTs of Dyspnoea at rest, Orthopnea, Laryngeal dyspnoea, and Use of accessory respiratory muscles in the global safety database and dyspnoea exertional in the Clinical Trial database. Additionally, cases that were serious due to medically significant criterion were reviewed and included in a case series analysis and other comments of the PRAC rapporteur were addressed. The addendum SER was presented in Appendix 22.

16.2.3.1 Results and Discussion

No additional ICSRs were retrieved by the added search terms. A single MedDRA PT of Dyspnoea at rest (n=1) was co-reported in an ICSR retrieved under the original search strategy.

Cases serious due to medically significant criteria, and a case that was serious due to disability, are presented in a case series table in the SER addendum. No consistent diagnostic pattern was seen for ICSRs that did not fall into categories of anaphylaxis or myocarditis/pericarditis.

16.2.3.2 Conclusion

A causal association between dyspnoea as a unique medical concept and Nuvaxovid remained not supported and the signal of dyspnoea remained refuted.

16.2.4 Tinnitus

A signal of "Tinnitus" was validated on 14-Nov-2022, pursuant to PRAC's request in their assessment of PBRER V 1.0 (20-Dec-2021 to 19-Jun-2022). Additionally, on 20-Dec-2022 a request for label update for tinnitus from TGA, Australia was received. The request was to update the Product Information to include tinnitus in Section 4.8 (Adverse Effects). A complete signal evaluation was performed, and the SER was presented in bi-monthly SSR No.02 and PBRER No.02.

On 07-Mar-2023, a request was received from PRAC, pursuant to their preliminary assessment of bimonthly SSR No.02 (9th SSR, period covering 16-Nov-2022 to 15-Jan-2023). The following is the supplementary information requested by PRAC for the signal of tinnitus:

- Discuss possible pathophysiological mechanisms that may underlie tinnitus following the administration of Nuvaxovid. Preclinical data and literature should be considered.
- Provide a causality analysis of all serious and non-serious cases reporting tinnitus.

Supplementary information was reviewed for the previously confirmed signal of tinnitus and the addendum SER was presented in Appendix 23.

16.2.4.1 Results and Discussion

See Appendix 23 for the detailed description of results.

16.2.4.2 Conclusion

Tinnitus remained to be a confirmed signal and CCDS V 7.0 already reflects tinnitus as an undesirable effect in post-marketing experience. No further actions are planned as of DLP.

16.2.5 Sensorineural Hearing Loss

A signal of sensorineural hearing loss was validated on 15-Jun-2023, pursuant to TGA request and a complete signal evaluation was performed. Relevant safety data from clinical trials and the post-authorization safety database was comprehensively reviewed to determine whether the available evidence supports or refutes a causal association between Nuvaxovid and sensorineural hearing loss. The signal was refuted following assessment, shortly after DLP of this report (on 30-Jul-2023). The SER is presented in Appendix 24.

16.2.5.1 Results and Discussion

No imbalance related to sensorineural hearing loss was identified from the clinical trial data. The search strategy yielded 19 reports of sensorineural hearing loss in the post-authorisation safety database. Six ICSRs concerned males, 13 ICSRs females, and among these individuals, the mean age was 48 years with range from 22 to 73 years. Most reports originated from Australia (n=6), Germany (n=4), and France (n=3). Frequently co-reported PTs comprised Tinnitus (n=6), headache (n=5), Malaise (n=3), Vaccination site pain (n=2), Ear discomfort (n=2), Vision blurred (n=2), Fatigue (n=2), Migraine (n=2), Feeling abnormal (n=2), and Paraesthesia (n=2). Positive rechallenge of Sudden hearing loss was noted in 2 reports. Seven reports had unilateral hearing loss, while 3 reports had bilateral hearing loss. Neurological manifestations were observed in 9 individuals (Paraesthesia, Encephalitis, Loss of consciousness, Vertigo, Tinnitus). Time to onset was 0-10 days in most cases (n=11, 58%). Often the outcome of the event was not recovered/not resolved (n=10), then recovering/resolving (n=4) and recovered/ resolved (n=3) as well as recovered with sequelae (n=1). Additionally, the overall and age-stratified O/E ratios were significantly lower than 1, indicating sensorineural hearing loss was not associated with receipt of NUVAXOVID vaccine.

16.2.5.2 Conclusion

Clinical trial events were balanced across treatment and placebo arms with no signals detected across the pivotal 2019nCoV-301 study. Of the 19 post-authorisation cases identified by the search strategy, 10 ICSRs had confounders including evidence of concurrent infection, underlying autoimmune disease, tachycardia possibly associated with stress or anxiety, and history of traumatic deafness. Importantly, the overall and age-stratified O/E ratios were significantly lower than 1, indicating that reports of sensorineural hearing loss are not above the expected incidence. The current evidence does not support a causal association between Nuvaxovid and sensorineural hearing loss.

16.2.6 EMA Inspection Requests

The EMA Inspection in Jan-2023 noted the following:

- Retrospective signal evaluation has not been performed following the grant of L2B access to NVX in the summer of 2022.

- The dates included in the signal tracker for signal identification, validation, etc., did not match the information given in the SER.

In response to the inspection findings, NVX downloaded L2B case information for the previously validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus.

L2B case information was also downloaded for the previous non-validated signals of angina pectoris, hypertension, Herpes Zoster and oral herpes in response to the same EMA Inspection finding as mentioned above.

The following methodology was used for review:

- L2B cases were downloaded based on a case list for each signal according to the established search strategy for the signal and significant and nonsignificant follow-up information was added to individual cases in the safety database.
- Following L2B case updates, the original query was re-run across the safety database, capturing all follow-up information added to the original cases.
- Cases with Initial Receipt Date on or before the DLP of the original SER with L2B updates were identified, new information was reviewed, and a determination was made regarding whether or not the new information would influence original results.

An update to the SER of Myocarditis and Pericarditis was generated with the correct date of validation, which will align with the signal tracker.

16.2.6.1 Results and Discussion

L2B downloads did not yield any significant information on previously non-validated signals of herpes zoster, oral herpes and angina pectoris. L2B download data obtained for the previously non-validated signal of hypertension and validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus did not change the disposition of the signal status. The addendum SERs for all the validated signals for the L2B download data are presented in Appendix 25.

The updated SER of myocarditis/pericarditis with the correct date of validation that aligns with the signal tracker is also presented in Appendix 26.

16.2.6.2 Conclusion

None of the information retrieved by the L2B downloads resulted in a change of disposition of these previously validated and non-validated signals. The signals of Herpes Zoster, oral herpes, angina pectoris and hypertension remain non-validated. The signals of anaphylaxis, myocarditis/pericarditis, paraesthesia and tinnitus remain confirmed and the signals of chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea and dyspnoea remain refuted with no further actions warranted from NVX.

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 V 2.1.

The EU Summary of Product Characteristics (SmPC) variation to include myocarditis and/or pericarditis was approved on 25-Oct-2022. Myocarditis and/or pericarditis will remain 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 15.3.17 for the O/E analysis.

- Narrow search strategy: Standardised MedDRA Query (SMQ) (Narrow): Noninfectious myocarditis/pericarditis; HLTs: Noninfectious myocarditis; Noninfectious pericarditis.
- Broad search strategy: SMQ (Broad): Noninfectious myocarditis/pericarditis; HLTs: Infectious myocarditis; Infectious pericarditis; Noninfectious myocarditis; Noninfectious 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 both the narrow and broad search strategies 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 NUVAXOVID administration and the presence of any alternative etiologies.

Twenty-five ICSRs (21 initial and 4 follow-ups) were retrieved with the broad search strategy during the reporting interval. Cumulatively, the broad search strategy yielded 120 ICSRs reporting events of myocarditis and/or pericarditis. Fifty-four ICSRs concerned males and 66 ICSRs concerned females. Most cases originated from Australia (n=71), Germany (n=14), United States (n=7), Italy (n=6), and South Korea (n=5). Frequently co-reported PTs comprised chest pain (n=55), pericarditis (n=50), dyspnoea (n=26), myocarditis (n=22), palpitations (n=20), fatigue (n=18), chest discomfort (n=15), headache (n=15), and dizziness (n=13). Recurrent myocarditis/pericarditis was noted in 18 cases. Four reports met BC case definition Level 1, 30 Level 2, 9 Level 3, and 4 Level 1 – 3 (exact level unknown). TTO was 0 – 7 days in the majority of cases (n=69, 57.5%). Often the outcome of the event (myocarditis/pericarditis and co-reported

PTs) was unknown (n=68) or not recovered/not resolved (n=66). Patient demographics are summarised in Table 32.

Report characteristics are summarised in Table 33. Published data for myocarditis cases from South Korea is included in Table 34. Although limited information was available to NVX for the 4 ICSRs received from the South Korean regulatory authority, review of aggregate data received from KDCA indicated that these 4 ICSRs were adjudicated by KDCA against a modified algorithm based on the Brighton Collaboration case definition and were confirmed myocarditis. Therefore these 4 ICSRs in the NVX safety database were considered as Level 1 – 3 (exact level unknown) cases.

Table 32: Demographics of Myocarditis and Pericarditis Report (Cumulative)

Sex/Age	Narrow Search Strategy (n=79) [a]		Broad Search Strategy (n=120)		Reports Meeting a Case Definition (Level 1 – 3; Broad Search Strategy) (n=47)	
	Number of Reports	% of Total	Number of Reports	% of Total	Number of Reports	% of Total
Male	**38**	**48.1%**	**54**	**45.0%**	**22**	**46.8%**
12 – 17	0	0.0%	0	0.0%	0	0.0%
18 – 29	16	20.3%	19	15.8%	6	12.8%
30 – 39	7	8.9%	12	10.0%	7	14.9%
40 – 49	9	11.4%	11	9.2%	6	12.8%
50 – 59	4	5.1%	6	5.0%	2	4.3%
60+	1	1.3%	3	2.5%	0	0.0%
UNK	1	1.3%	3	2.5%	1	2.1%
Female	**41**	**51.9%**	**66**	**55.0%**	**25**	**53.2%**
12 – 17	0	0.0%	0	0.0%	0	0.0%
18 – 29	11	13.9%	14	11.7%	4	8.5%
30 – 39	8	10.1%	14	11.7%	5	10.6%
40 – 49	11	13.9%	15	12.5%	4	8.5%
50 – 59	5	6.3%	10	8.3%	8	17.0%
60+	5	6.3%	10	8.3%	4	8.5%
Adult	0	0.0%	1	0.8%	0	0.0%
UNK	1	1.3%	14	11.7%	0	0.0%

[a] ICSRs retrieved with the narrow search strategy are incorporated into the O/E analysis.

Table 33: Report Characteristics for Myocarditis and Pericarditis (Cumulative)

Report Characteristic		Narrow Search Strategy (n=79) [a]		Broad Search Strategy (n=120)		Reports Meeting a Case Definition (Level 1 – 3; Broad Search Strategy) (n=47)	
		Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports
Total Reports Retrieved		79	100.0%	120	100.0%	47	100.0%
Reports Meeting a Case Definition		28	35.4%	47	39.2%	47	100.0%
Country of Incidence	Australia	54	68.4%	71	59.2%	28	59.6%
	Germany	9	11.4%	14	11.7%	6	12.8%
	United States	3	3.8%	7	5.8%	0	0.0%
	Italy	2	2.5%	6	5.0%	2	4.3%
	Korea, Republic of	5	6.3%	5	4.2%	5	10.6%
	Finland	0	0.0%	3	2.5%	1	2.1%
	Austria	0	0.0%	3	2.5%	2	4.3%
	France	3	3.8%	3	2.5%	3	6.4%
	Japan	1	1.3%	3	2.5%	0	0.0%
	New Zealand	1	1.3%	2	1.7%	0	0.0%
	United Kingdom	1	1.3%	1	0.8%	0	0.0%
	Luxembourg	0	0.0%	1	0.8%	0	0.0%
	Sweden	0	0.0%	1	0.8%	0	0.0%
Seriousness Criteria [b]	Medically Significant	79	100.0%	100	83.3%	37	78.7%
	Hospitalisation	25	31.6%	35	29.2%	14	29.8%
	Life-threatening	2	2.5%	3	2.5%	1	2.1%
	Fatal	1	1.3%	1	0.8%	0	0.0%

Table 33: Report Characteristics for Myocarditis and Pericarditis (Cumulative)

Report Characteristic		Narrow Search Strategy (n=79) [a]		Broad Search Strategy (n=120)		Reports Meeting a Case Definition (Level 1 – 3; Broad Search Strategy) (n=47)	
		Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports
Co-reported PTs [c]	Chest pain	55	45.8%	55	45.8%	24	51.1%
	Pericarditis	50	63.3%	50	41.7%	14	29.8%
	Dyspnoea	18	22.8%	26	21.7%	13	27.7%
	Myocarditis	22	27.8%	22	18.3%	10	21.3%
	Palpitations	14	17.7%	20	16.7%	9	19.1%
	Headache	9	11.4%	15	12.5%	9	19.1%
	Electrocardiogram abnormal	8	10.1%	12	10.0%	8	17.0%
	Dizziness	7	8.9%	13	10.8%	8	17.0%
	Fatigue	11	13.9%	18	15.0%	6	12.8%
	Chest discomfort	10	12.7%	15	12.5%	6	12.8%
	Arthralgia	9	11.4%	11	9.2%	5	10.6%
	Myalgia	6	7.6%	11	9.2%	5	10.6%
	Troponin increased	3	3.8%	6	5.0%	4	8.5%
	Pyrexia	7	8.9%	10	8.3%	4	8.5%
	Cardiovascular disorder	4	5.1%	4	3.3%	4	8.5%
	Tachycardia	6	7.6%	9	7.5%	4	8.5%
	Myopericarditis	6	7.6%	6	5.0%	4	8.5%
	Nausea	4	5.1%	9	7.5%	4	8.5%
	Extrasystoles	1	1.3%	11	9.2%	3	6.4%
	Supraventricular tachycardia	0	0.0%	3	2.5%	3	6.4%
	Troponin	3	3.8%	3	2.5%	3	6.4%

Table 33: Report Characteristics for Myocarditis and Pericarditis (Cumulative)

Report Characteristic		Narrow Search Strategy (n=79) [a]		Broad Search Strategy (n=120)		Reports Meeting a Case Definition (Level 1 – 3; Broad Search Strategy) (n=47)	
		Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports
	Paraesthesia	5	6.3%	7	5.8%	3	6.4%
	Hypertension	3	3.8%	6	5.0%	3	6.4%
	Pericardial effusion	4	5.1%	5	4.2%	3	6.4%
	Arrhythmia	2	2.5%	7	5.8%	3	6.4%
	Asthenia	3	3.8%	7	5.8%	3	6.4%
	Abdominal pain	3	3.8%	5	4.2%	3	6.4%
Recurrent Myocarditis/ Pericarditis [d]		15	19.0%	18	15.0%	5	10.6%
Reports Meeting a Case Definition [e]	Level 1	4	5.1%	4	3.3%	4	8.5%
	Level 2	18	22.8%	30	25.0%	30	63.8%
	Level 3	2	2.5%	9	7.5%	9	19.1%
	Level 1 – 3 (exact level unknown) [g]	4	5.1%	4	3.3%	4	8.5%
Time to Onset [f]	0 – 7	46	58.2%	69	57.5%	23	48.9%
	8 – 14	10	12.7%	15	12.5%	8	17.0%
	≥ 15	11	13.9%	17	14.2%	7	14.9%
	UNK	12	15.2%	19	15.8%	9	19.1%
Event Outcome (as reported in Initial Report) [h]	Unknown	52	65.8%	68	56.7%	24	51.1%
	Not Recovered/ Not Resolved	42	53.2%	66	55.0%	27	57.4%
	Recovering/ Resolving	16	20.3%	24	20.0%	13	27.7%
	Recovered/ Resolved	11	13.9%	26	21.7%	10	21.3%
	Recovered with Sequelae	2	2.5%	3	2.5%	2	4.3%

Table 33: Report Characteristics for Myocarditis and Pericarditis (Cumulative)

Report Characteristic		Narrow Search Strategy (n=79) [a]		Broad Search Strategy (n=120)		Reports Meeting a Case Definition (Level 1 – 3; Broad Search Strategy) (n=47)	
		Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports	Number of Reports	Percentage of Total Reports
	Fatal	1	1.3%	1	0.8%	0	0.0%

[a] ICSRs retrieved with the narrow search strategy are incorporated into the O/E analysis.

[b] Reflects case level seriousness, ICSRs may meet more than one seriousness criterion.

[c] PTs reported in > 5% of cases in reports meeting a case definition are included here.

[d] 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.

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

[f] 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 SSR.

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

[h] The outcome for all PTs in the retrieved ICSRs is summarized in this section.

Data from South Korea, which was published in the COVID-19 Vaccine Safety Report (Week 116; 26-Feb-2021 to 21-May-2023), indicated that of the 971,309 cumulative vaccinations, four confirmed cases of myocarditis (adjudicated against a modified algorithm based on the Brighton Collaboration case definition) were reported from 26-Feb-2021 to 18-May-2023. As mentioned above these four cases align with the four ICSRs received from the South Korean regulatory authority to the NVX safety database. Please see Table 34 below.

Table 34: Characteristics of Myocarditis cases in South Korea

Number of Vaccinations	**Total**				
	Diagnosed	**Dose of vaccination**		**Sex**	
	Cases	**1st Dose**	**Winter Season Additional Dose**	**Male (n=2)**	**Female (n=2)**
971,309	4	3	1	Age Range: 20 – 29 years and 40 – 49 years	Age Range 20 – 29 years and 50 – 59 years

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 characterization.

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 AESI and further information can be referenced in Section 15.3.25.

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:

During the reporting interval and cumulatively, anaphylaxis and tinnitus were identified risks for Nuvaxovid that were not categorised as important.

16.3.4.1 Tinnitus

Tinnitus was newly identified as a non-important risk during the reporting interval and was added to Section 4.8 (undesirable effects) of CCDS V 7.0, dated 02-Feb-2023. No significant safety information was received during the reporting interval that would alter its already

established characterization. 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 Results and Discussion

Use in Pregnancy:

Six ICSRs were retrieved for the interval (5 initial and 1 follow-up).

Cumulatively, 12 ICSRs were retrieved (12 females, age range 21 – 57 years). Out of the 12 cumulative ICSRs, 11 ICSRs included 12 pregnancy associated AEs (5 serious and 7 non-serious) and were coded to PTs of Maternal exposure during pregnancy (n=5), Abortion spontaneous (n=4), Exposure during pregnancy (n=2) and Pre-eclampsia (n=1). Pregnancy was reported as part of medical history in the 12th ICSR.

Out of the 12 ICSRs, 5 ICSRs were retrospective pregnancy reports, 4 were prospective pregnancy reports while the pregnancy report type is unknown for the remaining 3 reports. An analysis could not be performed as gestational age, obstetric details, medical history, concomitant medication, and further details were unknown. None of the 12 reports of use in pregnancy raises any safety concerns.

Use while breastfeeding:

One initial ICSR was retrieved for the interval.

Cumulatively, 3 ICSRs were retrieved (3 females, ages 29, 30 and 38 years, respectively). The 3 cumulative ICSRs included 3 non-serious AEs coded to PTs Exposure via breast milk (n=1), Lactation puerperal increased (n=1) and Lactation insufficiency (n=1).

16.3.5.1.2 Conclusion

None of the reports of use during pregnancy and breastfeeding raised any safety concerns.

No safety signal was identified.

16.3.5.2 Update on Missing Information: Use in Immunocompromised Patients

Nuvaxovid has not been studied in individuals with immunocompromised conditions, except for subjects with HIV.

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

One initial ICSR was retrieved for the interval.

Cumulatively, 5 ICSRs were retrieved (4 females and 1 male, age range 44 – 93 years). The 5 cumulative ICSRs included 19 AEs including 1 serious and 18 non-serious AEs. The PTs in these immunocompromised patients belong to the SOCs of Gastrointestinal disorders (n=6, non-serious), Skin and subcutaneous tissue disorders (n=3, non-serious), nervous system disorders (n=3, 1 serious and 2 non-serious), Eye disorders (n=2, non-serious), Respiratory, thoracic and mediastinal disorders (n=2, non-serious), General disorders and administration site conditions (n=2, non-serious) and Injury, poisoning and procedural complications (n=1, non-serious).

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)

Nuvaxovid has not been studied in frail individuals with comorbidities that may compromise immune function due to the condition or treatment of the condition. There is a concern that frail patients with comorbidities are potentially at risk of developing a more severe manifestation of COVID-19.

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

One-hundred thirty-seven ICSRs were retrieved for the interval (119 initial and 18 follow-ups).

Cumulatively, 519 ICSRs were retrieved (370 females, 138 males, 11 individuals of unspecified sex, age range 16 – 96 years when reported). The 519 cumulative ICSRs included 2,317 AEs including 581 serious (including 20 fatal AEs) and 1,736 non-serious AEs. The most frequently reported PTs (n>30) were Headache (n=103), Fatigue (n=100), Pyrexia (n=60), Myalgia (n=55), Chest pain (n=49), Dizziness (n=48), Nausea (n=43), Pain in extremity (n=41), Arthralgia (n=40), Malaise (n=38), Chills (n=37), Pain (n=33), Dyspnoea (n=32), Paraesthesia (n=32), Palpitations (n=32) and COVID-19 immunisation (n=32). Most reports were of individuals above the age of 40 years (n=319, 61.6%). The outcome of the majority of events was reported as not recovered at the time of reporting (n=824, 35.6%).

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

Thirty-five ICSRs were retrieved for the interval (29 initial and 6 follow-ups).

Cumulatively, 163 ICSRs were retrieved (137 females, 26 males, age range 21 – 94 years when reported). The 163 cumulative ICSRs included 789 AEs including 209 serious (including 18 fatal AEs) and 580 non-serious AEs. The most frequently reported PTs (n>20) were Headache (n=39), Fatigue (n=29) and Pyrexia (n=26). Most reports were of individuals above the age of 40 years (n=126, 77.3%). The outcome of the majority of events was reported as not recovered at the time of reporting (n=281, 35.6%).

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 the 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

No ICSRs were retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (female, 46 years). The report retrieved was manually reviewed for any vaccines listed in the non-company co-suspect field or concomitant drugs field. After assessment, it was identified that this report did not meet the inclusion criteria.

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 summarized in Appendix 8 Table 41.

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 latest version of EU RMP, V 3.1 that was approved on 06-Feb-2023.

16.5 Effectiveness of Risk Minimisation

Not applicable. There are no additional risk minimisation measures in place for Nuvaxovid. Routine risk minimisation activities are considered to be sufficient for monitoring all important identified risks, important potential risks and missing information.

17 BENEFIT EVALUATION

17.1 Important Baseline Efficacy and Effectiveness Information

The following information on efficacy of Nuvaxovid at the beginning of the reporting interval is from the CCDS in effect at the start of the reporting interval, V 6.0 (effective 10-Aug-2022) in Appendix 2.

The clinical efficacy, safety, and immunogenicity of Novavax COVID-19 Vaccine (recombinant, adjuvanted) is being evaluated in two pivotal, placebo-controlled, Phase 3 studies, 2019nCoV-301 conducted in North America and 2019nCoV-302 conducted in the UK.

17.1.1 Study 1 (2019nCoV-301) – Two-Dose Primary Series

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 USA and Mexico and a pediatric expansion occurring in participants 12 through 17 years of age in the USA.

Participants 18 Years of Age and Older

Upon enrollment in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive Novavax COVID-19 Vaccine (recombinant, adjuvanted) or placebo.

The primary efficacy analysis population (referred to as the Per-Protocol Efficacy [PP-EFF] analysis set) included 25,452 participants who received either Novavax COVID-19 Vaccine (recombinant, adjuvanted) (n=17,312) or placebo (n=8,140), received two doses (Dose 1 on day 0; Dose 2 at day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through 7 days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received vaccine 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 ≥ 30 kg/m2, chronic lung disease, diabetes mellitus type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrollment that occurred during the time period when strains classified as Variants of Concern or Variants of Interest were predominantly circulating in the two countries (USA 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.

Efficacy in Adolescents 12 through 17 Years of Age

The assessment of efficacy and immunogenicity of Novavax COVID-19 Vaccine (recombinant, adjuvanted) in adolescent participants 12 through 17 years of age occurred in USA 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 was the predominant variant circulating in the USA and accounted for all cases where sequence data are available (11/20, 55%).

17.1.2 Study 2 (2019nCoV-302) – Two Dose Primary Series

2019nCoV-302 is an ongoing Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the UK. Upon enrollment, participants were stratified by age (18 to 64 years; 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.

Elderly Population

Novavax COVID-19 Vaccine (recombinant, adjuvanted) was assessed in individuals 18 years of age and older. The efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years).

17.2 Newly Identified Information on Efficacy and Effectiveness

Newly identified information on the efficacy of NVX-CoV2373 that became available during the reporting interval was provided in final Clinical Summary Reports for two completed clinical trials and from the literature for one ongoing clinical trial.

17.2.1 Newly Identified Information on Efficacy and Effectiveness from Completed Clinical Trials

Section 7.1 of this PBRER summarized newly identified information on the efficacy of NVX-CoV2373 that became available during the reporting interval from final clinical study reports for two completed clinical trials – Study 2019nCoV-302 and Study 2019nCoV-501.

17.2.2 Newly Identified Information on Efficacy and Effectiveness from the Literature

Newly identified information from the literature on the efficacy of NVX-CoV2373 became available during the reporting interval in a publication about ongoing Study 2019nCoV-301 Adult Main (Primary Series). Efficacy in the per-protocol population required a PCR-positive SARS-CoV-2 test conducted at the study central laboratory, which led to the exclusion of COVID-19-associated hospitalizations lacking a positive PCR test result at the central laboratory. A post-hoc analysis of NVX-CoV2373 efficacy for an expanded population comprising COVID-19–associated hospitalisations diagnosed by any PCR test, rapid antigen test, or unspecified diagnostic test but without a PCR test result from the study central laboratory, demonstrated efficacy against hospitalisation was 100% (95% CI: 83.1, 100) (Marchese 2023).

17.3 Characterisation of Benefits

17.3.1 Adult Participants

In adult participants ≥ 18 years of age following primary series vaccination, the primary efficacy objective of the pivotal Phase 3 Clinical Study 2019nCoV-301 was achieved, with a vaccine efficacy of NVX-CoV2373 to prevent PCR-confirmed symptomatic mild, moderate, or severe COVID-19 of 90.40%, after 96 cases were accrued. The vaccine was also shown to be efficacious against variants that were either considered variant of concern/variant being monitored (92.92%) or not considered variant of concern/variant being monitored (100.0%) and specifically against the B.1.1.7 (Alpha) variant (93.09%). The vaccine was also observed to be efficacious in preventing moderate or severe COVID-19, with no NVX-CoV2373 recipient experiencing a severe event with an onset from at least 7 days after second vaccination (eg, Day 28).

The participant population of Clinical Study 2019nCoV-301 included adult participants ≥ 18 years of age who, by virtue of age, race, ethnicity, or life circumstances were considered at substantial risk of exposure to and infection with SARS-CoV-2. Efforts were made to prioritize the enrollment of participants ≥ 65 years of age, participants < 65 years of age with co-morbidities (ie, obesity, chronic kidney or lung disease, cardiovascular disease, and diabetes mellitus type 2), who were at higher risk of complications due to COVID-19. Participants were also considered at high risk if their living or working conditions involved known frequent exposure to SARS-CoV-2 or to densely populated circumstances (factory or meat packing plants, essential retail workers, etc). Vaccine efficacy was also demonstrated in subgroup analyses of these at-risk populations.

The immunogenicity of NVX-CoV2373 was evaluated in Clinical Study 2019nCoV-301 (Adult Main Study and Pediatric Expansion) and was supportive of the efficacy of the vaccine in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 as demonstrated in the pivotal Phase 3 study. In Clinical Study 2019nCoV-301, a two-dose regimen of NVX-CoV2373, administered 21 (+ 7) days apart, induced robust immune responses, with markedly increased wild-type virus (ancestral Wuhan strain) neutralizing antibody, serum IgG antibody, hACE2 receptor binding inhibition antibody levels relative to placebo in adult participants ≥ 18 years of age regardless of baseline serostatus. Cell-mediated immunity responses for the Th1 and Th2 cytokine pathways were evident following a 2-dose regimen of NVX-CoV2373, with responses skewed toward the Th1 cytokine pathway; suggesting reduced risk for vaccine-enhanced disease.

Following a homologous booster vaccination with NVX-CoV2373 ≥ 6 months after the second vaccination in the primary series, robust immune responses to the ancestral Wuhan strain (anti-S protein IgG, hACE2 receptor binding inhibition, neutralizing antibody), that exceeded peak responses observed after second vaccination in the primary series vaccination. In addition, a single booster dose of NVX-CoV2373 demonstrated cross-reactivity of the immune response

(serum IgG antibodies and neutralizing antibodies) to the Omicron BA.1 subvariant and the Omicron BA.5 subvariant (pseudovirus neutralizing antibodies) at 28 days after booster vaccination. As the immune responses following boosting vaccination were notably higher than those associated with high levels of efficacy after primary vaccination, these findings suggest that homologous boosting vaccination with NVX-CoV2373 should bolster protection against SARS-CoV-2 and its current variants/subvariants.

Following a heterologous booster vaccination with NVX-CoV2373 ≥ 6 months after receipt of 2 or 3 doses of authorized COVID-19 vaccine manufactured by Pfizer/BioNTech or Moderna, robust increases in anti-S protein IgG and neutralizing antibody titers were demonstrated in study 2019nCoV-307. Similar increases in antibody titers were noted in the COV-BOOST study in which individuals who had been primed with either the Pfizer/BioNTech vaccine or the AstraZeneca vaccine received a booster dose approximately 2.5 to 5 months following priming. The COV-BOOST study also indicated that a heterologous booster dose of NVX-CoV2373 was able to boost cellular immune responses.

17.3.2 Adolescent Participants

In adolescent participants 12 to < 18 years of age following primary series vaccination, the primary effectiveness objective of the Pediatric Expansion of Clinical Study 2019nCoV-301 was successfully demonstrated as non-inferior neutralizing antibody responses in adolescent participants 12 to < 18 years of age compared to young adults (18 to < 26 years of age) with all 3 pre-specified non-inferiority criteria simultaneously met: 1) the upper bound of two-sided 95% CI for the ratio of GMTs ($GMT_{18<26yo}/GMT_{12<18yo}$) was < 1.5: geometric mean ration 0.7, 95% CI: 0.6, 0.8.; 2) the point estimate of the ratio of GMTs was ≤ 1.22 (estimated as square root of 1.5): GMR 0.7, 95% CI: 0.6, 0.8; and 3) the upper bound of the two-sided 95% CI for difference of seroconversion rates ($SCR_{18<26yo} - SCR_{12-<18yo}$) was < 10%: seroconversion rate difference 1.1, 95% CI: -0.2, 2.8. The result of the primary efficacy objective in adolescent participants showed a vaccine efficacy of NVX-CoV2373 for preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 of 79.82% (95% CI: 47.54, 92.23) after 20 cases were accrued at a time when the predominant variant circulating variant in USA was the B.1.617.2 (Delta) variant.

NVX-CoV2373 also induced robust immune responses to the ancestral Wuhan strain (neutralizing antibody, serum IgG antibody, hACE2 receptor binding inhibition antibody levels) relative to placebo in adolescent participants 12 to < 18 years of age. As was observed in adult participants, a NVX-CoV2373 homologous booster ≥ 5 months after the first dose of the primary series vaccination elicited robust immune responses to the ancestral Wuhan strain (hACE2 receptor binding inhibition and neutralizing antibody), that exceeded peak responses observed after second vaccination in the primary series vaccination and demonstrated cross-reactivity of the immune response (serum IgG antibodies) to the Omicron BA.1 and BA.5 subvariants.

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 February 2020, the WHO designated the disease coronavirus disease 2019 or COVID-19. The virus that causes COVID-19 is designated SARS-CoV-2. COVID-19 has spread rapidly despite stringent efforts at control via quarantine. Several variants of concern (Alpha, Delta, Omicron etc.) have emerged since the original Wuhan strain, which are more transmissible and can cause severe disease or spread more rapidly. Significant health risks are associated with COVID-19 infection including a higher rate of mortality among patients with chronic medical conditions and weakened immune systems. Nearly two years later, SARS-CoV-2 transmission remains high, partly due to the emergence of multiple variant strains of the virus. As per WHO Coronavirus (COVID-19) dashboard (WHO 2023), globally, as of 12:23pm CEST, 07-Jun-2023, there have been 767,750,853 confirmed cases of COVID-19, including 6,941,095 deaths reported.

As of 6-Jun-2023, a total of 13,396,086,098 vaccine doses have been administered globally. Despite this vaccination rate, 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.

NVX developed recombinant protein vaccine formulated with the saponin-based Matrix-M adjuvant for the prevention of disease caused by SARS-CoV-2. Immunogenicity and protective efficacy of SARS-CoV-2 rS with Matrix-M adjuvant against wild-type SARS-CoV-2 virus have been established across several animal models and clinical trials including late-stage clinical trials.

In the wake of emerging SARS-CoV-2 variants, NVX has initiated the production and investigation of rS nanoparticle vaccines adjuvanted with Matrix-M adjuvant using the sequenced genomes from the B.1.351 (Beta) variant (product name: NVX-CoV2438), B.1.617.2 (Delta) variant (product names: NVX-CoV2464 and NVX-CoV2465), and B.1.1.529 (Omicron) variant (product name: NVX-CoV2515) viruses, and a bivalent SARS-CoV-2 rS nanoparticle vaccine combining the prototype Wuhan-Hu-1 strain and B.1.351 (Beta) variant. All the SARS-CoV-2 rS vaccine constructs being developed by NVX feature targeted mutations to improve resistance to proteolytic cleavage and enhance retention of the prefusion conformation. All bind to the hACE2 receptor with high affinity and exhibit good thermostability.

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 (i.e., Kineret) (EMA 2022a).

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), Vaxzevria (AstraZeneca), Spikevax (Moderna), Jcovden (Janssen), COVID-19 vaccine (Valneva) and VidPrevtyn Beta (Sanofi Pasteur) (EMA 2022b).

In addition, two monoclonal antibodies (i.e., Evusheld and Ronapreve) are authorised for prevention of COVID-19 (EMA 2022a). General preventative measures include social distancing, face masks, and proper hygiene.

There is a public health need to promote equitable access to the COVID-19 vaccines, by providing more traditional protein-based vaccines as an alternative to the vaccine technologies such as mRNA and that may improve vaccine uptake in parts of the world where cold chain technologies are not that established.

18.2 Benefit-Risk Analysis Evaluation

Based on the totality of the data across the SARS-CoV-2 rS clinical development program, NVX-CoV2373 administered as either 2 intramuscular injections at least 21 days (+ 7 days) apart as primary series vaccination or 1 intramuscular injection at approximately 6 months after the completion of primary series vaccination 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 both neutralizing antibody titers and cellular immune responses.

The benefits of Nuvaxovid have been established across the clinical development program and are reflected in the current global labelling. Overall, the new evidence on efficacy and effectiveness obtained during the current reporting period supports the findings from previous studies which formed the basis of the benefit profile for Nuvaxovid described in the RSI.

The safety profile of SARS-CoV-2 rS has been well characterized on the basis of controlled clinical study data from more than 47,395 participants exposed to SARS-CoV-2 rS with a median follow-up of approximately 1 year. The safety data shows that Nuvaxovid has an acceptable safety profile.

In addition, the consistency of immunogenicity and safety of 3 different lots of NVX-CoV2373 in previously vaccinated adult participants has been well demonstrated in a Phase 3 study, 2019nCoV-307 that is completed during the reporting interval, suggesting that NVX-CoV2373 is immunogenic regardless of whether it is used as a first booster or later booster dose, and whether it follows earlier doses of NVX-CoV2373 or other authorized vaccines. Additionally, it displayed immunogenicity against all 3 tested variants of SARS-CoV-2 (Wuhan strain, BA.1 and BA.5 subvariants).

Important risks that are recognised with Nuvaxovid include myocarditis and/or pericarditis (important identified risk) and vaccine associated enhanced disease including vaccine associated enhanced respiratory disease (important potential risk). The EU RMP was updated during the reporting interval to V 3.1 (dated 06-Feb-2023) with no change in the summary of safety concerns. The important potential risks and missing information are managed with routine risk minimisation measures in the Product Information (as applicable) and monitored via routine and additional pharmacovigilance activities described in the EU RMP. There are no safety concerns requiring additional risk minimisation measures. Based on the available safety and efficacy data, the overall benefit risk profile of Nuvaxovid remains favorable.

NVX will continue to review the safety of Nuvaxovid including all the reports of adverse experience and will revise the product documents if an evaluation of the safety data yields significant new information.

19 CONCLUSION

During the reporting interval, signal of menstrual disorders rechallenge has been refuted and closed and the signal of sensorineural hearing loss was validated. Based on scientific evaluation of the available information, the signal of sensorineural hearing loss was refuted and closed after the DLP.

Supplementary information for previously validated signals of diarrhoea, dyspnoea and tinnitus was reviewed. Additionally, L2B case details were downloaded from EudraVigilance for previously validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, acute coronary syndrome associated with hypersensitivity, diarrhoea, dyspnoea and tinnitus and non-validated signals of angina pectoris, hypertension, herpes zoster and oral herpes. The reviews were completed after the DLP and did not influence original evidence supporting confirmation/refutation of the signals.

Cumulatively, signals of anaphylaxis, paraesthesia/ hypoaesthesia, tinnitus and myocarditis and pericarditis have been confirmed, and the CCDS has been updated to include paraesthesia/hypoaesthesia and tinnitus in Section 4.8 (Undesirable effects) of V 5.0 dated 21-Jul-2022 and V 7.0 dated 02-Feb-2023 respectively. Anaphylaxis and myocarditis and pericarditis were added to Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 of the CCDS V 5.0 dated 21-Jul-2022 and V 6.0 dated 10-Aug-2022 respectively.

During the reporting interval, NVX has received authorisations for adolescents and booster indications in additional countries.

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 V 7.0, dated 02-Feb-2023) for Nuvaxovid. The data contained within this report support the conclusion that the overall benefit-risk balance for Nuvaxovid continues to remain positive.

NVX will continue to monitor the safety data from all sources for new emerging signals and changes to known safety concerns according to pharmacovigilance activities established for COVID-19 vaccines.

20 APPENDICES