NUVAXOVID: Periodic safety update report assessment

20th June 2022 to 19th December 2022

This document consists of:

1. The PRAC assessment report of the NUVAXOVID periodic safety update report (PSUR) covering the period 20th June 2022 to 19th December 2022, 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/300620/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010972/202212

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

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

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	9 March 2023	9 March 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	8 May 2023	8 May 2023
☐	MS/PRAC members and MAH comments	7 June 2023	7 June 2023
☐	PRAC Rapporteur's updated assessment report following comments	22 June 2023	21 June 2023
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	6 July 2023	6 July 2023

Procedure resources	
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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*.

Whenever the above box is un-ticked please indicate the section and page where the confidential information is located here:

Confidential information:

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1. Background information on the procedure

This is the assessment of a periodic safety update report (PSUR) 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 second periodic benefit-risk evaluation report (PBRER) for Nuvaxovid (NVX-CoV2373) covers the interval between 20 June 2022 and 19 December 2022. On 20 December 2021, the vaccine was granted conditional marketing authorisation by the European Medicines Agency (EMA) for the active immunisation to prevent Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). During the reporting interval, Nuvaxovid received additional authorisations for adults, adolescents, homologous and heterologous booster indications. It is now approved as a primary series vaccine in individuals 12 years and older and as a booster dose in adults.

The number of NVX-CoV2373 doses distributed globally in the reporting interval is estimated to be 63,765,380 doses (54,436,730 Nuvaxovid and 9,328,650 Covovax), and the cumulative number to be 103,799,960 doses (94,471,310 Nuvaxovid and 9,328,650 Covovax). Thereof, 1,338,871 NVX-CoV2373 doses were administered in Australia, Canada, the European Union (EU), India, Israel, Japan, New Zealand, Singapore, Switzerland, South Korea, Taiwan and the United States of America (USA) in the reporting interval and 2,393,247 doses cumulatively.

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

For the cumulative period up to 19 December 2022, signals of anaphylaxis, myocarditis/pericarditis, paraesthesia/hypoaesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and other rhythm abnormalities, and acute coronary syndrome associated with hypersensitivity were closed following evaluation. Signals of anaphylaxis, myocarditis and/or pericarditis and paraesthesia/hypoaesthesia were confirmed. The company core data sheet (CCDS) was updated to include anaphylaxis in section 4.4, paraesthesia/hypoaesthesia in section 4.8, myocarditis and pericarditis in sections 4.4 and 4.8, and paraesthesia/hypoaesthesia in section 4.8. On 01 September 2022, the core (EU) risk management plan (RMP) was updated to reclassify myocarditis and pericarditis from an important potential risk to an important identified risk. This EU RMP was approved on 01 December 2022.

During the reporting interval, the MAH refuted the signals of diarrhoea, dyspnoea, syncope, menstrual disorders, and tachycardia with other rhythm abnormalities, and confirmed the signal of tinnitus. The signal evaluation reports on diarrhoea, dyspnoea, and tinnitus had been submitted with the 9th summary safety report (SSR) covering the period between 16 November 2022 and 15 January 2023. 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.

According to the MAH, 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.

No updates to the product information are deemed necessary at this time, nor additional risk minimisation measures. 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 NVX-CoV2373 remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR or as a post-authorisation measure (PAM) [1]

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

1. Information on age, sex and racial/ethnic group of individuals exposed to NVX-CoV2373 within clinical trials should be provided.
2. Cumulative summary tabulations in the present PSUR are not well understandable. The MAH is therefore asked to choose an intuitively comprehensible way of presentation in subsequent PSURs and to define column headings like "-".

4. PSUR frequency

☒ No changes to the PSUR frequency

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

[1] The submission of PAMs for CAPs must be done in eCTD format via the eSubmission Gateway/Web Client, and will be considered delivered to all National Competent Authorities representatives, alternates and scientific experts. PAMs must not be submitted to the PSUR Repository.

Annex: final PRAC rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

The MAH presents the second periodic benefit-risk evaluation report (PBRER) for Nuvaxovid, i.e. NVX-CoV2373™ dispersion for injection Coronavirus disease 2019 (COVID-19) vaccine (recombinant, adjuvanted) (SARS-CoV-2rS). 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 PBRER covers the interval between 20 June 2022 and 19 December 2022.

Nuvaxovid is a recombinant, adjuvanted protein vaccine indicated for the active immunisation to prevent 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 in individuals 12 years of age and older – as Covovax for individuals 7 years and older – and as a booster dose in adults. It is a suspension for intramuscular injection and supplied in a multidose container of 10 doses of 0.5 mL each.

The MAH does not propose changes to the product information as part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

Under the invented names Nuvaxovid and Covovax, the vaccine has been authorised in several countries and regions (PBRER pp. 213-216, Appendix 3, Table 29), first on 31 October 2021 in Indonesia (Covovax). Nuvaxovid is approved as a primary series vaccine in individuals 12 years and older and as a booster dose in adults. In India, Covovax is authorised as a primary series vaccine for individuals 7 years and older.

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

Table 1: Invented names and countries/region of authorisation (adapted from PBRER pp. 213-216, Appendix 3, Table 29). UK, United Kingdom; USA, United States of America; WHO, World Health Organisation.

Rapporteur assessment comment:

The World Health Organisation (WHO) is not a country/region. During the reporting interval, new or expanded authorisations were received in Australia, Canada, EU, India, Israel, Japan, New Zealand, South Africa, South Korea, Switzerland, Taiwan, UK, and USA (alphabetical, not chronological order).

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

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

1.3.2. Changes to reference safety information

The reference safety information (RSI) is the company core data sheet (CCDS) version 6.0, dated 10 August 2022. During the reporting interval, the RSI was updated following the confirmation of signals for anaphylaxis, paraesthesia and hypoaesthesia (type II safety variation approved on 06 September 2022), as well as myocarditis and pericarditis (type II safety variation approved on 25 October 2022). Besides, three version updates were made to the CCDS to include the adolescent indication and the homologous booster dose following the two-dose primary series.

V4.0	27-Jun-2022	Section 4.8 Undesirable Effects Deleted injection site swelling (19%) and injection site redness (17%) under subheading Adolescents 12 through 17 years of age–after two-dose primary series to align with updated data of an Erratum to the pediatric expansion interim CSR from study 2019nCoV-301 approved on 29-Apr-2022 with the table 14.3.2.3.6 Summary of Solicited Reactions by Maximum Toxicity Grade Among Grades 1 or Higher 7 Days Following Any Vaccination Safety Analysis Set.
V5.0	21-Jul-2022	Section 4.4: Special Warnings and Precautions Updated sub-section 4.1.1 Hypersensitivity and anaphylaxis to amend the sentence to "Events of anaphylaxis have been seen with Novavax COVID-19 Vaccine (Recombinant, Adjuvanted)." Section 4.8 Undesirable Effects Updated to add sub-section post-marketing experience and Table (2) for post-marketing events. anaphylaxis as an immune system disorder, and hypoaesthesia and paraesthesia as nervous system disorders, with unknown frequency, are added to Table 2.
V 6.0	10-Aug-2022	Section 4.4 and Section 4.8 were updated to include Myocarditis and Pericarditis. Section 6.3 was updated to reflect extended in-use duration from 6 -12 hours post needle puncture.

Table 2: CCDS summary of changes (PBRER p. 31, Table 1).

Rapporteur assessment comment:

The MAH provides an overview of changes to the RSI during the reporting interval. It does not propose new safety information or key risk minimisation recommendations.

1.3.3. Estimated exposure and use patterns

Exposure in clinical trials

According to the MAH, a cumulative total of 46,171 subjects received at least one dose of NVX-CoV2373 in the clinical development program.

Treatment	Estimated Total Number of Subjects Exposed (> 18 years of age)[a]
NVX-CoV2373	43,839
Placebo (normal saline)	8,386
ICC (qNIV + NVX-CoV2373)	558
NVX-CoV2515	317
NVX-CoV2373+ NVX-CoV2515	317

a: Includes final study data from 2019nCoV-101 (Part1), 2019nCoV-101 (Part2), 2019nCoV-301 Adult, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311, 2019nCoV-501, 2019nCoV-505 and 2019nCoV-ICC-E-101.

Table 3: Estimated cumulative clinical trial exposure in adults (PBRER p. 32, Table 2).

Age group	Treatment[a]	
	NVX-CoV2373	Placebo
≥ 6 months to < 12 years	**180**	**100**
≥ 12 years to < 18 years (inclusive)	2,152	80

a: Includes data from 2019nCoV-301, adolescent sub-study and 2019nCoV-503 study.

Table 4: Estimated cumulative clinical trial exposure in paediatric and adolescent subjects (PBRER p. 32, Table 3).

Rapporteur assessment comment:

A differentiation by sex (PBRER p. 32, Table 4) and racial/ethnic group (PBRER p. 33, Table 5) is made for only 108 adult individuals from the final 2019nCoV-101 (part 1) clinical study report. Whether these are representative of the other 46,063 study participants remains unclear. Contrary to what is stated, there is no breakdown by age – only data for persons of at least 18 years of age are shown. The MAH is kindly requested to provide this information in the next PBRER.

Exposure from post-authorisation experience

Data cut-off dates for administration and distribution data are not identical for the different countries/regions and are displayed in Table 6 of the PBRER (pp. 34-35). When available, they range between 31 August and 19 December and 30 November and 18 December 2022, respectively.

Dose	Actual Doses Administered [a]	Adjusted doses including re-allocated doses [b]	Calculated Doses Administered [c]	Total Estimated Doses Administered [d]
Interval				
First Dose	142,981	151,411	6,601	158,012
Second Dose	132,115	139,998	6,601	146,599
Booster Dose	1,060,969	1,064,748	8,800	1,073,548
Unknown Dose Number	16	0	0	0
Interval Total	1,338,871	1,358,947	22,002	1,380,949
Cumulative				
First Dose	514,707	552,324	6,601	558,925
Second Dose	382,518	405,648	6,601	412,249
Booster Dose	1,493,059	1,498,787	8,800	1,507,587
Unknown Dose Number	19	0	0	0
Cumulative Total [e]	2,393,247	2,459,703	22,002	2,481,705

[a] Data presented as recorded. No assumptions or adjustments were made regarding this data. All countries with administration data are presented in this column. Refer to list of countries with administration data.

[b] Column represents administration data re-allocated to first and second dose only (refer to calculations above Table 8 this is used for calculating total estimated administration doses for O/E analysis). All countries with administration data are presented in this column. For a list of countries for which this re-allocation was applied, refer to text above Table 8

[c] Column represents administration data derived from distribution data. This was only done for Singapore. Assumptions applied to derive administered doses from distribution data are presented in Appendix 10.

[d] Column represents all estimated administration doses utilised in the O/E analysis. This column is a summation of columns b and c. All countries with either administration data or distribution 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

Table 5: Interval and cumulative estimated exposure data (administered) from post-authorisation experience (PBRER p. 37, Table 8).

According to PBRER Table 9 (p. 38), when known, most doses were administered to adults.

Total Doses Actually Administered [a,b,c]			
Dose	**Paediatrics**	**Adults**	**Elderly**
Interval			
First Dose	59	11,101	6,493
Second Dose	60	13,587	7,175
Third/Booster Dose	80	63,339	24,065
Interval Total	199	88,027	37,733
Cumulative			
First Dose	152	152,814	21,000
Second Dose	123	111,294	16,607
Third/Booster Dose	145	115,779	39,489
Cumulative Total	420	379,887	77,096

Note: Data Sources and cut-off dates are presented in Table 6.

[a] Data presented as recorded. The list of countries that included age data within the available administration data are presented in the text above.

[b] Some countries in the EU (Table 7) did not provide age categories consistently as per 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.

Table 6: Interval and cumulative actual exposure data (administered) by age group from post-authorisation experience (PBRER p. 38, Table 9).

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

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Interval		
Australia (Biocelect Pty Ltd) [b]	78,953	14,371,700
Canada (NVX) [b]	4,071	6,485,900
EU (NVX) [b]	38,999	20,466,860
India (SIIPL) [c]	27,348	120,650
Indonesia (SIIPL) [c]	NA	9,008,000
Israel (Medicalix/Freyr) [b]	5	1,000,000
Japan (Takeda) [b]	251,404	4,597,210
New Zealand (Biocelect New Zealand Ltd.) [b]	3,135	756,000
Singapore (PharmaEng Technology Pte Ltd) [b]	18,073	111,000
South Korea (SK Bioscience) [b]	345,993	901,760
Switzerland (NVX) [b]	2,426	502,000
Taiwan (NVX) [b]	502,493	1,008,000
Thailand (SIIPL) [c]	Not available	200,000
UK (NVX) [b]	Not available	1,000,000
USA (NVX) [b]	65,971	3,236,300
Interval Total	1,338,871	63,765,380
Interval Total Covovax	27,348	9,328,650
Interval Total Nuvaxovid	1,311,523	54,436,730

Table 7: Interval exposure data (administered and distributed) from post-authorisation experience presented by region/license partner (PBRER p. 38-39, 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]	235,549	21,236,300
Canada (NVX) [b]	11,087	9,724,000
EU (NVX) [b]	345,231	42,946,850
India (SIIPL) [c]	27,348	120,650
Indonesia (SIIPL) [c]	Not Available	9,008,000
Israel (Medicalix/Freyr) [b]	5	1,000,000
Japan (Takeda) [b]	269,922	8,238,590
New Zealand (Biocelect New Zealand Ltd.) [b]	7,039	2,031,800
Singapore (PharmaEng Technology Pte Ltd) [b]	18,073	615,000
South Korea (SK Bioscience) [b]	908,103	2,932,470
Switzerland (NVX) [b]	2,426	502,000
Taiwan (NVX) [b]	502,493	1,008,000
Thailand (SIIPL) [c]	Not Available	200,000
UK (NVX) [b]	Not Available	1,000,000
USA (NVX) [b]	65,971	3,236,300
Cumulative Total	2,393,247	103,799,960
Cumulative Total Covovax	27,348	9,328,650
Cumulative Total Nuvaxovid	2,365,899	94,471,310

Table 8: Cumulative exposure data (administered and distributed) from post-authorisation experience presented by region/license partner (PBRER p. 39, Table 10). a, data presented as recorded; b, Nuvaxovid; c, Covovax; LP, license partner.

Rapporteur assessment comment:

The MAH estimates that approximately 56% of all doses cumulatively administered (1,380,949 out of 2,481,705 doses) were applied during the reporting interval, particularly as booster doses (1,073,548 out of 1,507,587 booster doses, i.e. 71% of all cumulative booster doses).

According to Table 10 of the PBRER, 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.

Looking at the 9th summary safety report (SSR) with the administration data cut-off date 15 January 2023, a considerable increase in the number of doses administered in EU is noticeable. Cumulative doses administered, 9th SSR, data cut-off 15 January 2023: 158,735 (Germany) and 347,461 (EU without Germany). Cumulative doses administered, 2nd PBRER, data cut-off 19 December 2022: 345,231 (EU including Germany).

1.3.4. Data in summary tabulations

The MAH addresses serious adverse events (SAEs) from studies 2019nCoV-101 (part 1 and part 2), 2019nCoV-301, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311, 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 NVX-CoV2373 with Matrix-M adjuvant or placebo and experienced a total of 1,916 SAEs. The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) fell under the system organ classes (SOCs) of "infections and infestations" (434 PTs), "cardiac disorders" (222 PTs), and "respiratory, thoracic and mediastinal disorders" (151 PTs).

Post authorisation, the MAH states having received a cumulative total of 3,161 spontaneous individual case safety reports (ICSRs) reporting 12,430 adverse events (AEs), thereof 1,927 serious and 10,503 non-serious. During the 6-month reporting interval, 1,363 spontaneous ICSRs were received – of which 69 ICSRs were follow-ups – with 4,950 AEs, thereof 755 serious unlisted, 259 serious listed, 2,222 non-serious unlisted, and 1,714 non-serious listed.

According to the MAH, 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 this PBRER. As of 04 December 2022, a cumulative total of 908,103 Nuvaxovid doses were administered in South Korea, with a corresponding total of 1,215 AEs. The five most commonly reported symptoms (PBRER pp. 42-43, Table 11) included myalgia (n = 259 cases), headache (n = 243), dizziness (n = 171), chest pain (n = 165), and allergic reaction (n = 160). Three cumulative cases of myocarditis resulted in an incidence rate of 0.3 cases per 100,000 vaccinations. From 26 February 2021 to 22 November 2022, six anaphylaxis cases were confirmed to have causal relationship with the administration of Nuvaxovid, five of which involved female vaccinees. Six cases (including duplicates) of vaccine associated enhanced disease (VAED) were reported. The MAH notes that it does not have access to the ICSRs and there are no other cases in the global post-marketing setting, so it considers the evidence insufficient to suggest that VAED constitutes a safety signal. A fatal outcome was described in seven cases. The MAH concludes that the aggregate data from South Korea are consistent with the known safety profile of Nuvaxovid, and that its review did not identify new signals.

Rapporteur assessment comment:

Appendix 4 lists MedDRA SOCs and PTs of SAEs observed in clinical trials, separately by study. For study 2019nCoV-101, part 2, 48 SAEs are listed, 47 of which are in the "blinded" column and one (PT "musculoskeletal chest pain") in the "-" column. Whether "-" corresponds to the placebo group remains unclear. In the table for the 2019nCoV-301 study, it also remains unclear what the "-" column means. The total number of SAEs ("total" column) is not the sum of the SAEs in the "blinded," "study product (test drug)" and "-" columns. Also, the majority of SAEs are listed in the "-" column, which would be surprising given a 2:1 randomisation of vaccine to placebo and the assumption that "-" corresponds to the placebo group. Taken together, the column "total" gives 1,916 SAEs, the column "blinded" 237, the column "study product (test drug)" 135 and the column "-" 1,648 SAEs. In the data for study 2019nCoV-302 (1:1 randomisation of vaccine to placebo), it is remarkable that more COVID-19 SAEs are reported in the "study product (test drug)" column (COVID-19, n = 9; COVID-19 pneumonia, n = 14) than in the "placebo/vehicle" column (COVID-19, n = 2; COVID-19 pneumonia, n = 7). All in all, the summary tabulation is not well understandable for the assessor. The MAH is therefore asked to choose an intuitively comprehensible way of presentation in subsequent PBRERs and to define column headings like "-".

Appendix 5 provides summary tabulations of serious and non-serious PTs from post-authorisation data sources. Of a total of 12,420 AEs, 3,569 are listed under the SOC "general disorders and administration site conditions", 2,241 under the SOC "nervous system disorders", 1,350 under the SOC "musculoskeletal and connective tissue disorders", 820 under the SOC "gastrointestinal disorders", 646 under the SOC "skin and subcutaneous tissue disorders", 624 under the SOC "respiratory, thoracic and mediastinal disorders", 607 under the SOC "cardiac disorders", and 368 under the SOC "infections and infestations". Of 1,926 spontaneously reported SAEs, 1,013 (53%) were reported during the reporting interval, and 3,930 (37%) of 10,494 non-serious AEs. This proportion is tolerable in view of the fact that 56% of all

doses administered post-marketing were applied during the reporting interval. However, some PTs were now described more frequently; e.g., 13 of 15 myocarditis events and 5 of 6 myopericarditis events were from the reporting interval.

As far as assessable on the basis of the information available, 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, no clinical studies were completed for NVX-CoV2373. Table 31, Appendix 7, lists the completed company-sponsored study 2019nCoV-101 (part 1).

Ongoing clinical trials

According to the MAH, there were no emerging safety findings reported from the nine ongoing company-sponsored clinical trials during the reporting interval. Table 32, Appendix 7, lists the ongoing company-sponsored studies 2019nCoV-101 (part 2), 2019nCoV-301 (adult part), 2019nCoV-301 (adolescent extension), 2019nCoV-302, 2019nCoV-307, 2019nCoV-501, 2019nCoV-505, 2019nCoV-311, and the 2019nCoV-503 paediatric study.

The MAH presents data on the immunogenicity of different dose regimens in the study **2019nCoV-101, part 2**. With regards to safety, healthy adults aged 18 to 84 years tolerated well up to 4 doses of the vaccine including Matrix-M adjuvant. Multiple vaccinations were more frequently and to a greater extent associated with solicited local and systemic reactions. SAEs were reported in 39 (3.0%) subjects overall. For study **2019nCoV-301** in adults, the MAH provides data on vaccine efficacy and safety. NVX-CoV2373 recipients reported higher frequencies and intensities of solicited injection site and systemic adverse reactions than placebo recipients, especially after the second vaccination of the initial vaccination period. Tenderness and pain were the most frequently reported solicited injection site reactions and fatigue, headache, muscle pain, and malaise were the most frequently reported systemic adverse reactions. The MAH notes that there were similar frequencies and intensities of unsolicited AEs among both NVX-CoV2373 and placebo recipients during the initial vaccination period, with the exception of unsolicited AEs of the SOC "general disorders and administration site conditions" which had a higher frequency among NVX-CoV2373 recipients than placebo recipients, largely attributable to reactogenicity reactions. In study **2019nCoV-301 Adult Booster**, tenderness and pain were the most frequent (incidence > 10%) solicited local treatment emergent adverse events (TEAEs) and muscle pain, fatigue, headache, malaise, arthralgia, and nausea/vomiting were the most frequent solicited systemic TEAEs. Solicited local and systemic TEAEs were reported more frequently in the younger age group (18-64 years) than in the older age group (≥ 65 years). In study **2019nCoV-301 Adolescent Booster**, solicited local and systemic TEAEs were reported in 80.5% and 85.8% of adolescent subjects, respectively, with the majority of subjects (59.5%) reporting events of grade 1 or grade 2 severity and with tenderness and pain (local) and headache, fatigue, muscle pain, malaise, and nausea/vomiting (systemic) being the most frequent (incidence > 25% subjects). Unsolicited TEAEs among the 220 subjects of the restricted population through 28 days after the third (booster) dose of NVX-CoV2373 were reported in 11 (5.0%) adolescent subjects. Among the 1,499 subjects of the unrestricted population through 28 days after the third (booster) dose of NVX-CoV2373, unsolicited TEAEs were reported in 77 (5.1%) adolescent subjects. Study **2019nCoV-302** showed that the durability of vaccine efficacy of NVX-CoV2373 to protect against PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second vaccination in either the initial or blinded crossover vaccination period waned over time, ranging from 86.5% (95% confidence interval [CI]: 78.1, 91.7) at the start of the surveillance period to 28.9% (95% CI: -16.2, 56.4) at 6 months after the start of the surveillance period. Immune response was higher in the younger

age cohort comprising subjects 18 to 64 years of age than the older age cohort. The frequency, intensity, and duration of solicited local and systemic TEAEs increased after second vaccination relative to the first vaccination. After dose 2, tenderness and pain were the most frequent solicited local TEAEs in the two study vaccine groups, with 924 (76.7%) and 968 (80.4%) subjects, respectively, in the NVX-CoV2373 group and 164 (14.0%) and 200 (17.1%) subjects in the placebo group. Subjects in the older age cohort (65 to 84 years of age) reported a lower frequency and intensity of solicited local and systemic TEAEs than subjects in the younger age cohort (18 to 64 years of age). Severe TEAEs occurred in 122 (1.6%) subjects in the NVX-CoV2373 group and 99 (1.3%) subjects in the placebo group, with severe treatment-related TEAEs reported in 43 (0.6%) subjects in the NVX-CoV2373 group and 12 (0.2%) subjects in the placebo group. One TEAE (myocarditis) in the NVX-CoV2373 group was assessed as related by the investigator (but not by the sponsor) to study vaccine. The study **2019nCoV-307** with the aim to compare the immunogenicity of three lots of NVX-CoV2373 in adults met the primary endpoint by demonstrating equal immunogenicity between the three lots. According to the MAH, safety across the three lots was comparable and was consistent with the known safety profile of NVX-CoV2373. In study **2019nCoV-501**, vaccine efficacy for prevention of PCR-confirmed symptomatic mild, moderate, or severe COVID-19 decreased initially from day 35 through month 6 (i.e., day 201) in the pre-crossover vaccination period and then increased from month 6 through day 386 following booster/post-crossover vaccinations in the booster/post-crossover vaccination period analysed overall in serologically naïve healthy adult human immunodeficiency virus (HIV)-negative subjects and medically stable persons living with HIV. The MAH notes that through month 12, a two-dose regimen consisting 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 subjects ≥ 18 to < 85 years of age and medically stable persons living with HIV ≥ 18 to < 65 years of age with 96.7% of subjects receiving both doses of NVX-CoV2373 (pre-crossover) and 97.8% of subjects receiving both doses of the post-crossover booster regimen. Pain and tenderness were the most frequently reported solicited local TEAEs; headache, fatigue, and muscle pain were the most frequently reported solicited systemic TEAEs. According to the MAH, unsolicited severe treatment-related TEAEs were due mainly to reactogenicity. For study **2019nCoV-503** in children 6 months to < 12 years of age, the MAH notes that no interim [analysis] was planned as of the data lock point of this PBRER. The same applies to study **2019nCoV-505** in people living with HIV and to study **2019nCoV-311** in adults.

Long-term follow-up

The MAH states that no new safety information became available from company-sponsored clinical trials.

Other therapeutic use of medicinal product

During the reporting interval, one compassionate use study was ongoing in South Africa for healthcare workers, as part of 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, a phase 1/2, randomised, observer-blind study (study 2019nCoV-ICC-E-101) to evaluate the safety and immunogenicity of a fixed combination of quadrivalent nanoparticle influenza vaccine (qNIV) and NVX-CoV2373 in healthy subjects ≥ 50 to ≤ 70 years of age was completed. According to the MAH, no significant safety findings were observed following the end of study review.

Non-interventional safety studies

The MAH states that no safety findings were reported from any non-interventional safety studies, that would have an impact on the benefit-risk profile of NVX-CoV2373. One post-authorisation safety study (PASS) was ongoing during the reporting interval. Study 2019nCoV-405 is the pregnancy registry C-VIPER, which has two patients enrolled through 30 November 2022. The two other safety studies listed in

Appendix 8, 2019nCoV-402 and 2019nCoV-404, still have the status "planned". The MAH notes that the feasibility assessment planned for study 2019nCoV-402 could not be conducted because "a significant amount of data accrued since May 2022 was missing from the Clinical Practice Research Datalink (CPRD) Aurum database".

Other clinical trials

The MAH states that during the reporting interval, there were no relevant new safety observations identified from any other studies that would change the benefit-risk balance of NVX-CoV2373. Table 33, Appendix 7, lists clinical trials conducted by license partners: TAK-019-1501, TAK-019-3001, IND 027485, ICMR/SII-COVOVAX CTRI/2021/02/031554, COVOVAX-Booster CTRI/2022/04/042017, and G42-HC-2021001. Table 34, Appendix 7, lists investigator-initiated studies: CoM-COV-2 (EudraCT 2021-001275-16), CoM-COV-3 (EudraCT 2021-004267-27), RHM MED1781 COV-Boost (Eudra CT 2021-002175-19), and OCTAVE-DUO 2021-003632-87.

Medication errors

In its global vaccine safety database, the MAH retrieved 105 ICSRs for the interval (103 initial and 2 follow-up) and 146 ICSRs cumulatively. The latter included 189 AEs, thereof one serious and 188 non-serious. The most common PTs reported were "interchange of vaccine products" (n = 23), "vaccination error" (n = 21), "inappropriate schedule of product administration" (n = 17), "incomplete course of vaccination" (n = 17), "product administration error" (n = 16), "product administered to patient of inappropriate age" (n = 15), "expired product administered" (n = 10), 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

The MAH states that during the reporting interval, there were no safety findings from non-clinical studies that impacted the benefit-risk profile of NVX-CoV2373. Table 13, pp. 94-96, summarises non-clinical studies either ongoing or completed during the reporting interval, with "no safety findings" in all studies.

Literature

During the reporting interval, the MAH identified 13 literature articles for NVX-CoV2373. 12 articles are briefly outlined. The MAH concludes that its literature review did not identify any new and/or significant safety findings that would impact the overall benefit-risk balance of NVX-CoV2373.

Other periodic reports

Table 14 lists periodic SSRs submitted to health authorities.

SSR No.	Reporting Interval	Data Lock Point
Nuvaxovid SSR No. 05	01-Jun-2022 to 30-Jun-2022	30-Jun-2022
Covovax SSR No. 10	01-Jun-2022 to 30-Jun-2022	30-Jun-2022
Nuvaxovid SSR No. 06	01-Jul-2022 to 31-Jul-2022	31-Jul-2022
Covovax SSR No. 11	01-Jul-2022 to 31-Jul-2022	31-Jul-2022
Nuvaxovid SSR No. 07	01-Aug-2022 to 31-Aug-2022	31-Aug-2022
Covovax SSR No. 12	01-Aug-2022 to 31-Aug-2022	31-Aug-2022
Nuvaxovid SSR No. 08	01-Sep-2022 to 30-Sep-2022	30-Sep-2022
Covovax SSR No. 13	01-Sep-2022 to 30-Sep-2022	30-Sep-2022
Nuvaxovid SSR No. 09	01-Oct-2022 to 31-Oct-2022	31-Oct-2022
Covovax SSR No. 14	01-Oct-2022 to 31-Oct-2022	31-Oct-2022
Nuvaxovid SSR No. 10 (Bimonthly)	01-Sep-2022 to 15-Nov-2022	15-Nov-2022
Nuvaxovid SSR No. 11	01-Nov-2022 to 30-Nov-2022	30-Nov-2022
Covovax SSR No. 15	01-Nov-2022 to 30-Nov-2022	30-Nov-2022

Table 9: Periodic summary safety reports submitted to health authorities (PBRER p. 104, Table 14).

Rapporteur assessment comment:

The MAH refers to nine ongoing studies, but lists ten studies. Study 2019nCoV-501 is not referenced in the outline. Besides, the MAH mentions 13 literature articles, but only briefly presents 12 of them. The reason for omitting one manuscript remains unclear. With regards to other periodic reports, the MAH does not make any content-related statements, but merely lists the numbers and periods of SSRs in a table. There is no relevant gain in information from this. The abbreviation "HA" is not explained either in the text or in the list of abbreviations. Overall, the MAH does not describe any new data relevantly questioning the safety of the vaccine.

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 were obtained from controlled clinical trials.

1.3.7. Late-breaking information

The MAH states that no significant late breaking information with reference to Nuvaxovid safety, efficacy and effectiveness has been received after the data lock point of this PBRER.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Summary of Safety Concerns	
Important identified risk(s)	None
Important potential risk(s)	VAED, including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis
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

Source: EU Risk Management Plan (EU-RMP) V1.2 dated 09-May-2022

Table 10: Summary of safety concerns at the beginning of the reporting interval (PBRER p. 150, Table 27). VAED, vaccine-associated enhanced disease.

The signal of myocarditis and pericarditis was confirmed on 03 August 2022 and the CCDS was updated to include myocarditis and pericarditis in sections 4.4 and 4.8. The risk of myocarditis and/or pericarditis was reclassified from an important potential risk to an important identified risk in the EU risk management plan (RMP) version 2.1 of 01 September 2022 (approved by EMA on 01 December 2022).

Summary of Safety Concerns	
Important identified risk	Myocarditis and/or pericarditis
Important potential risk	VAED, including vaccine-associated enhanced respiratory disease (VAERD)
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

Source : EU RMP v 2.1 dated 01-Sep-2022.

Table 11: Summary of safety concerns at the end of the reporting interval (PBRER p. 151, Table 28). VAED, vaccine-associated enhanced disease.

2.2. Signal evaluation

According to the MAH, diarrhoea, dyspnoea and tinnitus underwent signal evaluation during the reporting interval. Signals of anaphylaxis, myocarditis/pericarditis, paraesthesia/hypoaesthesia, chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, syncope, menstrual disorders, tachycardia and

other rhythm abnormalities, and acute coronary syndrome associated with hypersensitivity were closed following evaluation. Signals of anaphylaxis, myocarditis/pericarditis, and paraesthesia/hypoaesthesia were confirmed and the product information was updated via safety variation procedures. A CCDS update is planned for tinnitus.

Signal Term	Date Detected	Status (New, Ongoing, or Closed)	Signal Disposition (Confirmed, Refuted or Indeterminate)	Date Closed	Source of Trigger of Signal	Reason for Evaluation and Summary of Key Data	Method of Signal Evaluation	Action(s) Taken or Planned
Anaphylaxis	18-May-22	Closed	Confirmed	27-Jun-2022	Health Authority (TGA)/ EMA (SSR No. 03)	HA Request	Provided in SER submitted with SSR No.05	Added to Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable Effects) section of the CCDS V5.0. A safety variation was approved on 06-Sep-2022.
Myocarditis and Pericarditis	17-May-22	Closed	Confirmed	03-Aug-2022	Health Authority (TGA) /EMA (SSR No.03)	HA Request	Provided in SER submitted with SSR No.05	Added to Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable Effects) of the CCDS V6.0. A safety variation was approved on 25-Oct-2022.
Paraesthesia/ Hypoaesthesia	27-May-22	Closed	Confirmed	27-Jun-2022	Health Authority (TGA)/EMA (SSR No. 03)	HA Request	Provided in SER submitted with SSR No.05	Added to Section 4.8 (Undesirable Effects) of the CCDS V5.0. A safety variation was approved on 06-Sep-2022.
Chest Pain/Chest Discomfort	15-Jun-2022	Closed	Refuted	09-Aug-2022	Health Canada Request	HA Request	Provided in SER submitted with SSR No.06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Dizziness	15-Jun-2022	Closed	Refuted	05-Aug-2022	Health Canada Request	HA Request	Provided in SER submitted with SSR No.06	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Encephalitis/ Encephalomyelitis	16-Jun-2022	Closed	Refuted	05-Aug-2022	South Korea HA Request	HA Request	Provided in SER submitted with SSR No.06	This signal was refuted.
Menstrual disorders	27-Jun-2022	Closed	Refuted	05-Aug-2022	PRAC Request (SSR No.04)	HA Request	SER included in Appendix 25	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Tachycardia and other Rhythm Disorders	27-Jun-2022	Closed	Refuted	09-Aug-2022	PRAC Request (SSR No.04)	HA Request	SER included in Appendix 22	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Acute Coronary Syndrome Associated with Allergic Reaction	27-Jul-2022	Closed	Refuted	12-Sep-2022	PMDA Request (SSR No.05)	HA Request	SER included in Appendix 23	The signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Syncope	25-Jul-2022	Closed	Refuted	12-Sep-2022	PRAC Request (SSR No.05)	HA Request	SER included in Appendix 24	Syncope is adequately labeled in SmPC Section 4.4 (Special Warnings and Precautions for Use).
Diarrhoea	14-Nov-2022	New	Refuted	NA	PRAC Request (PBRER V 1.0)	HA Request	SER included in Appendix 19	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Dyspnoea	14-Nov-2022	New	Refuted	NA	PRAC Request (PBRER V 1.0)	HA Request	SER included in Appendix 20	This signal was refuted based on current available data from clinical trials and the post-authorisation setting.
Tinnitus	14-Nov-2022	New	Confirmed	NA	PRAC Request (PBRER V 1.0)	HA Request	SER included in Appendix 21	CCDS to be updated

Table 12: Tabular summary of safety signals new, ongoing, or closed during the reporting interval (PBRER pp. 326-328, Appendix 6, Table 30).

The MAH notes that following the data lock point, signal evaluation reports were completed for diarrhoea, dyspnoea, and tinnitus. These signals had been validated following the assessment of the first PBRER (EMEA/H/C/PSUSA/00010972/202206).

Anaphylaxis (closed signal)

Anaphylaxis has been included in sections 4.4 and 4.8 of the CCDS.
The MAH's query of its global vaccine safety database retrieved 24 ICSRs for the reporting interval (22 initial and 2 follow-up) and 44 ICSRs cumulatively. These 44 ICSRs included 44 AEs (all serious) coded to PTs "anaphylactic reaction" (n = 30), "circulatory collapse" (n = 6), "anaphylactic shock" (n = 4), "anaphylactoid reaction" (n = 2), "shock" (n = 1), and "type I hypersensitivity" (n = 1). Most ICSRs involved females (n = 38, 86.4%).
For the risk window 0-1 day, observed versus expected (O/E) analyses showed increased and statistically significant results for the 2nd dose (rate ratio [RR] 8.61, 95% CI: 2.35-22.04) and booster doses (RR 11.76, 95% CI: 6.59-19.40). Also for the risk window 0-2 days, the RR was increased for the 2nd dose and for the booster doses. For the risk window 0-7 days, a statistically significant RR of 2.47 (95% CI: 1.77-3.35) was found, but results by dose number were not increased. Besides, the MAH presents O/E analyses stratified by age and sex (PBRER p. 110, Table 17). The MAH points out limitations of the method due to incomplete demographic data available.

Myocarditis and pericarditis (closed signal)

The CCDS has been updated to include myocarditis and pericarditis in sections 4.4 and 4.8, and the risk of myocarditis and/or pericarditis has been reclassified from an important potential risk to an important identified risk in the EU RMP version 2.1.

With regards to myocarditis, 18 ICSRs were retrieved from the global vaccine safety database for the interval (11 initial and 7 follow-up), and 21 ICSRs were retrieved cumulatively (11 males, 9 females, 1 unspecified sex; age range 18-76 years, median age 32 years). These 21 ICSRs included 21 AEs (all serious) coded to the PTs "myocarditis" (n = 15) and "myopericarditis" (n = 6).
The MAH presents O/E analyses for the risk windows 0-7 days, 0-14 days, 0-30 days, and 0-42 days. For all risk windows, the observed rate showed an increase when compared to the expected rate with a statistically significant RR. When assessing by dose number, results were increased and statistically significant only for dose 2 and only for the risk window 0-7 days. When stratified by sex with a risk window of 0-42 days, O/E results were increased and statistically significant in both the female and the male groups. In addition to the general limitations mentioned in the last section, the MAH points out that there is a possibility of overestimation of observed myocarditis counts, since 9 AEs with unknown time to onset (TTO) were conservatively assessed as falling within the risk window.

With regards to pericarditis, 26 ICSRs were retrieved for the interval (12 initial and 14 follow-up), and 42 ICSRs were retrieved cumulatively (21 males, 21 females), using the narrow search strategy. These 42 ICSRs included 42 AEs (all serious) coded to the PT "pericarditis".
The MAH presents O/E analyses for the risk windows 0-7 days, 0-14 days, 0-30 days, and 0-42 days. For all risk windows, the observed rate showed an increase when compared to the expected rate with a statistically significant RR. When assessing by dose number, no O/E results were both increased and statistically significant. When accounting for all cumulative pericarditis reports, the crude observed rates as reported in the male and female groups showed a statistically significant increase when compared to the expected rates. The MAH points out that there is a possibility of overestimation of observed

pericarditis counts, since 13 AEs with unknown TTO were conservatively assessed as falling within the risk window.

Additionally, the MAH queried its global vaccine safety database for ICSRs using its prespecified search strategy for myocarditis and pericarditis, and retrieved 44 ICSRs (23 initial, 21 follow-up) during the reporting interval and 65 ICSRs cumulatively (32 females, 32 males, one individual of unspecified sex; age range 26-54 years, median age 37 years). These 65 ICSRs included 65 AEs (all serious) coded to PTs "pericarditis" (n = 42), "myocarditis" (n = 15), "myopericarditis" (n = 6), and "carditis" (n = 2).
The MAH presents O/E analyses for the risk windows 0-7 days, 0-14 days, 0-30 days, and 0-42 days. For all risk windows, the observed rate showed an increase when compared to the expected rate with a statistically significant RR. When assessing by dose number, no O/E results were both increased and statistically significant. When accounting for all cumulative myocarditis and pericarditis reports, the crude observed rates as reported in the male and female groups showed a statistically significant increase when compared to the expected rates. The MAH points out that there is a possibility of overestimation of observed myocarditis and pericarditis counts, as 23 AEs with unknown TTO were conservatively assessed as falling within the risk window.

Paraesthesia (closed signal)

Paraesthesia has been classified as an identified risk, and the CCDS has been updated to include paraesthesia/hypoaesthesia in section 4.8.
Using its prespecified search strategy for paraesthesia, the MAH's query in its global vaccine safety database retrieved 118 ICSRs (106 initial and 12 follow-up) during the reporting interval. Cumulatively, 358 ICSRs were retrieved (93 males, 264 females, 1 unknown sex, age range 13-81 years when reported) and included 444 AEs (thereof 57 serious) coded to PTs "paraesthesia" (n = 278), "hypoaesthesia" (n = 119), "burning sensation" (n = 30), "hyperaesthesia" (n = 9), "dysaesthesia" (n = 6) and "hemiparaesthesia" (n = 2).

Encephalitis and encephalomyelitis (closed signal)

The MAH had provided its signal evaluation review in the first PBRER and the 6th SSR; the signal had been refuted.
The MAH's broad search strategy yielded three initial ICSRs for the reporting interval. Cumulatively, four ICSRs were retrieved (3 females, 1 male; age range 42-67 years) and included four AEs (all serious) coded to the PTs "noninfective encephalitis" (n = 2), "encephalitis" (n = 1), and "encephalitis post immunisation" (n = 1).
The MAH notes that its O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

Chest pain and chest discomfort (closed signal)

The MAH's signal evaluation did not suggest any apparent patterns or trends that would identify specific diagnoses beyond the chest pain/discomfort that may potentially relate to listed events or other topics under review (hypersensitivity, vaccination anxiety-related events and myocarditis/pericarditis) or would not be anticipated in the general population, hence this signal was refuted.

Dizziness (closed signal)

According to the MAH, a complete signal evaluation was performed and did not reveal any trends or patterns suggesting a safety signal. The MAH states that in most cases, the constellation of co-reported symptoms may be associated with reactogenicity or anxiety and did not suggest a specific neurologic pattern, hence this signal was refuted.

Tachycardia and other rhythm abnormalities (closed signal)

The MAH notes that its signal evaluation did not identify any apparent trend or pattern. Besides, cases were confounded by concurrent events, some of which may related to the listed events including hypersensitivity or vaccination anxiety-related events. The MAH presents its signal evaluation review as of 09 August 2022 and additional clinical trial data as of 08 September 2022 in Appendix 22 of this PBRER.

Rapporteur assessment comment:

The signal of tachycardia and other rhythm abnormalities had been assessed in the 6th monthly safety update. The same report on the signal dated 09 August 2022 is included in the current PBRER, Appendix 22. However, following PRAC review of this report, the MAH had been asked to repeat the analysis of data from clinical trials, taking into account multiple time windows. In addition, case reports from clinical trials should be characterised more in detail with regard to the duration of the AE and its outcome. The MAH complied with this demand in the 7th SSR as requested and presented an addendum to its safety signal evaluation report dated 08 September 2022. In its assessment, the PRAC rapporteur endorsed the MAH's conclusion to refute the signal. Appendix 22 of the present PBRER does not provide any new data on the issue, so the PRAC rapporteur refrains from re-evaluating it.

Menstrual disorders (closed signal)

The MAH states that based on its comprehensive review of 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, the signal of menstrual disorders was refuted. It provides the signal evaluation review as of 05 August 2022 and addendum as of 07 September in Appendix 25 of this PBRER.
During the reporting interval and cumulatively, the MAH retrieved 40 initial and 106 ICSRs, respectively. These 106 ICSRs included 168 AEs (thereof 8 serious) coded to the PTs "menstrual disorder" (n = 47), "heavy menstrual bleeding" (n = 37), "dysmenorrhoea" (n = 16), "amenorrhoea" (n = 15), "menstruation irregular" (n = 14), "intermenstrual bleeding" (n = 12), "polymenorrhoea" (n = 9), "menstruation delayed" (n = 6), "oligomenorrhoea" (n = 5), "hypomenorrhoea" (n = 4), "menstrual discomfort" (n = 2), and "premenstrual pain" (n = 1).

Rapporteur assessment comment:

The signal of menstrual disorders had been evaluated in the 6th monthly SSR (signal evaluation report dated 05 August 2022). Subsequently, the MAH had been asked to repeat the analysis of clinical trial data focussing solely on exposed women of childbearing age and considering a normal cycle of up to 35 days. The MAH had provided an addendum dated 07 September 2022 with additional analysis in the 7th SSR, which had been endorsed by the PRAC. Although the total numbers were low, there were some imbalances in clinical trials between the vaccine and placebo groups for the MedDRA PTs "menstruation irregular" and "heavy menstrual bleeding" both in the pre- and post-cross-over period. Therefore, the MAH had been asked to carefully monitor menstrual disorders in subsequent safety reports. Following the assessment of the 8th SSR, the MAH had been asked to present cases of menstrual disorders with positive re-challenge. These data had been submitted with the 9th SSR. The PRAC rapporteur agreed with the MAH that the cases of one positive and one negative re-challenge 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 supported. Appendix 25 of the present PBRER does not provide any new data on the issue, so the PRAC rapporteur refrains from re-evaluating it.

Acute coronary syndrome associated with allergic reaction (closed signal)

The MAH refuted the signal following its signal evaluation and presents its signal evaluation review in Appendix 23 of this PBRER.

Rapporteur assessment comment:

In its 7th monthly safety report, the MAH presented its signal evaluation for acute coronary syndrome associated with allergic reaction, dated 08 September 2022. Its search using the standardised MedDRA queries (broad) "ischaemic heart disease" and "hypersensitivity" had identified only one report received until 18 August 2022. The signal was refuted and closed in September 2022, and no new information on the issue was provided since then.

Syncope (closed signal)

The MAH notes that based on its signal evaluation, it concluded that no additional signals or other aetiologies beyond events associated with vaccine administration and related anxiety reactions were identified beyond what is already listed in the summary of product characteristics (SmPC) section 4.4. The signal was refuted. The MAH's signal evaluation review as of 08 September 2022 is presented in Appendix 24 of this PBRER.

Rapporteur assessment comment:

The report on the signal syncope of 08 September 2022 had already been presented in the 7th SSR. The signal had been refuted and closed in September 2022. The present PBRER does not contain any new data on this topic.

Diarrhoea (new signal)

The signal evaluation report as of 13 January 2023 had already been provided in the 9th SSR. The following summary is taken from the corresponding assessment. The MAH states having performed a comprehensive review of the safety data relevant to the MedDRA PT "diarrhea" from clinical trials and the post-authorisation safety database.

Rapporteur assessment comment:

The MAH's query is quite narrow in scope. The PT "diarrhoea" does not cover some reactions, such as "diarrhoea haemorrhagic" (PT 10012741). A more comprehensive search, for example with the high level term (HLT) "diarrhoea (excl infective)", would have been appropriate here.

In its introduction, the MAH states that diarrhoea is a common phenomenon, with about 0.6 episodes per person per year in the USA. 11.5% of COVID-19 patients experience diarrhoea, and after vaccination against COVID-19, diarrhoea accounted for 3.1% of adverse events reported to the Centers for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS), e.g., after vaccination with Comirnaty (3.1%) or Spikevax (3.0%). Of these postvaccination diarrhoea cases, 14.9% resulted in hospitalisation and 1.9% in death. Concerning Nuvaxovid, diarrhoea is not a labeled event as per the current version of the CCDS (version 6.0; effective 10 August 2022).

In its signal evaluation report, the MAH notes that, cumulatively, 2,401,803 doses have been administered in Australia, Canada, EU, Israel, Japan, New Zealand, Singapore, South Korea, Switzerland, Taiwan, and the USA, and 29,710 Covovax doses in India (as of 31 December 2022). A total of 105,103,560 doses (95,771,310 Nuvaxovid and 9,332,250 Covovax doses) were distributed globally.

Methods: The MAH reviewed the clinical trial database for unsolicited AEs using the MedDRA PT diarrhoea. The search included unblinded data from studies 2019nCoV-301, 2019nCoV-302 and 2019nCoV-501. Further, it queried the global vaccine safety database for ICSRs reporting the MedDRA PT diarrhoea with

the data lock point 16 November 2022. The MAH states that, although BC case definition for diarrhoea is available, none of the serious ICSRs had details of frequency or consistency of stool, so none met any case criteria due to a lack of information.

Rapporteur assessment comment:

Review at the case level was performed exclusively for cases with seriousness criteria.

Results: The MAH did not observe group differences for the PT diarrhoea (system organ class [SOC] gastrointestinal disorders) in clinical trials. Tables 3-5 (SSR p. 3556, Appendix 21) give unsolicited AE reporting rates between <0.1% and 1.1% of participants in vaccine groups and between 0.2% and 0.9% in placebo groups. The search in the post-authorisation safety database yielded 93 ICSRs, thereof 78 (84%) non-serious. Time to onset of diarrhoea ranged from 0 to 7 days, when reported (56% of events). The most frequent co-reported PTs included "fatigue" (46%), "headache" (44%), "nausea" (42%), "pyrexia" (30%), "injection site pain" (28%), and "dizziness" (25%). The event outcome was not recovered/not resolved in 39 reports (42%). Most often, vaccinees between 40 and 49 years of age were affected (n = 28 cases, 30%; SSR p. 3559, Appendix 21, Table 7), as well as females (n = 75, 81%).

According to the MAH, EudraVigilance Data Analysis (EVDAS) electronic Reaction Monitoring Report (eRMR) data (16 December 2022 through 31 December 2022) showed a reporting odds ratio (ROR) of 0.52 with signal disproportionate reporting and Vaccine Adverse Event Reporting System (VAERS) data (03 December 2022 through 16 December 2022) showed an EB05 of 0.177 for the PT diarrhoea.

The MAH provides the narratives of the 15 cases that resulted in hospitalisation and/or disability and/or were determined to be medically significant (SSR pp. 3560-3575, Table 8). There were no life-threatening of fatal ICSRs reported. Causality was classified as inconsistent in one case and as indeterminate in the remaining 14 cases.

The MAH summarises that no specific aetiology or pattern has become evident. It concludes that its review of data does not support a causal association between Nuvaxovid and diarrhoea, and therefore refutes this signal.

Rapporteur assessment comment:

Given the small number of cases overall, all ICSRs could have been analysed in more detail. Nevertheless, the PRAC rapporteur can follow the MAH's arguments. From the data presented, there is currently no evidence to suggest that diarrhoea should be included in the SmPC. The reaction should continue to be monitored, if possible using a broader search strategy, and efforts should be made to obtain the most comprehensive data possible with regard to causality assessment.

Dyspnoea (new signal)

The signal evaluation report as of 12 January 2023 had already been provided in the 9th SSR. The summary is taken from the corresponding assessment. The MAH states having performed a comprehensive review of the safety data relevant to the MedDRA PT dyspnoea from clinical trials and to the MedDRA PTs "dyspnea" and "dyspnoea exertional" from the post-authorisation safety database.

Rapporteur assessment comment:

The MAH's search did not include reactions such as "dyspnoea at rest" (PT 10013969), "orthopnoea" (PT 10031123), "laryngeal dyspnoea" (PT 10052390), "use of accessory respiratory muscles" (PT 10069555), and, in the clinical trial database, "dyspnoea exertional" (PT 10013971). Due to the rather narrow search strategy, cases may have been missed.

Methods: The MAH reviewed the clinical trial database for unsolicited AEs using the MedDRA PT "dyspnea". The search included unblinded data from studies 2019nCoV-301, 2019nCoV-302 and 2019nCoV-501. Further, it queried the post-authorisation safety database for ICSRs reporting the MedDRA PTs "dyspnea" and "dyspnoea exertional" with the data lock point 30 November 2022. Cases with seriousness criteria of hospitalisation or death were reviewed at the case level.

Rapporteur assessment comment:

The MAH does not justify why only a subset of the cases reported as serious were examined in more detail. 66 of the 242 (27%) post-marketing ICSRs were reported to be "medically significant" but not further investigated by the MAH.

Results: The MAH did not observe group differences in clinical trials. Tables 3-5 (SSR pp. 3592-3593, Appendix 22) give unsolicited AE reporting rates between 0% and 0.3% of participants in vaccine groups and between <0.1% and 0.3% in placebo groups. The search in the post-authorisation safety database yielded 242 ICSRs of which 59 (24%) concerned males and 180 (74%) females. Vaccinees between 30 and 49 years of age were most frequently affected. 66 (27%) reports met the seriousness criterion "medically significant", and 24 (10%) cases involved hospitalisation. Disability and death were reported in one case each, and the seriousness criterion "other" was marked in four cases. The most frequent co-reported PTs were "chest pain" (n = 89 cases, 37%), "fatigue" (n = 74, 31%), "headache" (n = 64, 26%), "dizziness" (n = 61, 25%), "chest discomfort" (n = 51, 21%), "palpitations" (n = 50, 21%), and "paraesthesia" (n = 39, 16%). The event outcome was not recovered/not resolved and unknown in 138 (57%) and 74 (31%) cases, respectively.

Rapporteur assessment comment:

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 should specify whether only the outcome of the events "dyspnoea" and "dyspnoea exertional" is meant here.

The MAH notes overlap for events falling under anaphylaxis (standardised MedDRA query [SMQ] [narrow] "anaphylactic reaction") and myocarditis/pericarditis search strategies (SMQ [broad] "noninfectious myocarditis/pericarditis"; HLTs "infectious myocarditis", "infectious pericarditis", "noninfectious myocarditis", "noninfectious pericarditis"). Its myocarditis/pericarditis and anaphylaxis search strategies retrieved five and one ICSRs, respectively, coding the PTs "dyspnea" or "dyspnoea exertional". Table 8 (SSR pp. 3597-) lists the narratives of 25 ICSRs (10%).

Rapporteur assessment comment:

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.

In EVDAS (16 December 2022 to 31 December 2022), the MedDRA PT "dyspnoea" presented with a ROR of 2.02 and the PT "dyspnoea exertional" with a ROR of 2.46. According to the MAH, both PTs did not present a signal of disproportionate reporting. In VAERS, (03 December 2022 to 16 December 2022), the MedDRA PT "dyspnoea" presented an EB05 value of 0.347. The PT of "dyspnoea exertional" was not in VAERS.

The MAH points out that dyspnoea is not a labelled event, but included in the current version of the Nuvaxovid CCDS as a symptom of myocarditis or pericarditis. In cases associated with hospitalisation, co-reported symptoms may indicate reactogenicity or anxiety. The MAH emphasises that shortness of breath is a known symptom of anaphylaxis or hypersensitivity, and concludes that its review does not support a causal association between Nuvaxovid and dyspnoea.

Rapporteur assessment comment:

Unfortunately, a more detailed analysis was performed in only 10% of the post-marketing cases retrieved. Given the low total number of ICSRs, this is considered insufficient to draw the above conclusion. Furthermore, a rather narrow search strategy was chosen. The PRAC rapporteur agrees with the MAH that dyspnoea can be a symptom of several underlying conditions. Therefore, dyspnoea may not always be coded when the underlying condition is coded and the incidence of the symptom may be underestimated.

Tinnitus (new signal)

The signal evaluation report as of 13 January 2023 had already been provided in the 9th SSR. The summary here is taken from the corresponding assessment. In addition to the PRAC request on 14 November 2022 (procedure EMEA/H/C/PSUSA/00010972/202206), the MAH received a request from Therapeutic Goods Administration, Australia, on 20 December 2022 to update the product information to include tinnitus in section 4.8. The MAH states having performed a comprehensive review of the safety data relevant to the MedDRA PT "tinnitus" from clinical trials and the post-authorisation safety database.

In its introduction, the MAH points out that tinnitus is prevalent in the general population (worldwide prevalence 4.6 to 30%), may have a variety of aetiologies, including stress-related pathology, and has been reported with COVID-19 and following vaccination with mRNA COVID-19 vaccines and other vaccines. As per current version 6.0 of the CCDS (effective 10 August 2022), tinnitus is not a labelled event.

Table 2 (SSR p. 3635, Appendix 23) lists distributed and administered Nuvaxovid and Covovax doses by country or region. In total, the MAH assumes 104,248,420 distributed and 2,320,593 administered vaccine doses.

Methods: The MAH reviewed the clinical trial database for unsolicited AEs using the MedDRA PT "tinnitus". The search included unblinded data from studies 2019nCoV-301, 2019nCoV-302 and 2019nCoV-501. Further, it queried the post-authorisation safety database for ICSRs reporting the MedDRA PT "tinnitus" with the data lock point 30 November 2022. The MAH's review focused on cases that were serious due to criteria of death, hospitalisation, medically significant, disability and/or life-threatening.

Rapporteur assessment comment:

To query for PT "tinnitus" is considered appropriate.

Results: The MAH did not observe group differences in clinical trials. Tables 3-5 (SSR pp. 3637-3638, Appendix 23) give unsolicited AE reporting rates between 0% and 0.1% of participants in vaccine groups and between 0% and <0.1% in placebo groups. The search in the post-authorisation safety database yielded 67 ICSRs (15 serious, 52 non-serious), with 34 events (51%) experienced within five days of vaccination. Time to onset was unknown in 22 events (33%). The most frequent MedDRA PTs co-reported with tinnitus were "headache" (n = 21, 31%), fatigue (n = 13, 19%), "paraesthesia" (n = 12, 18%), and "dizziness" (n = 11, 16%). The outcome was reported as not recovered/not resolved in 39 cases (58%), unknown in 12 cases (18%), recovered/resolved in eight cases (12%), recovering/resolving in six cases (9%), and recovered with sequelae in two cases (3%). 23 reports (34%) concerned males, and 43 reports (64%) females. The age group between 30 and 39 years was most frequently affected (n = 18 cases, 27%). The narratives of the 15 serious events, thereof five associated with disability, two with hospitalisation, one with other medically important condition and seven medically significant, are presented in Table 8 (SSR pp. 3642-3647, Appendix 23). The MAH's analysis of these cases did not support a pattern or causal association due to the presence of confounding factors or alternative explanations for the event.

According to the MAH, a disproportionality analysis of EVDAS eRMR report (01 December 2022 through 15 December 2022) showed a ROR of 3.35, with a changed status to "increased".

The MAH sums up that tinnitus has been reported following vaccination with Nuvaxovid in a pattern consistent with typically associated stress or anxiety-related vaccination reactions. It states that "case-level (qualitative) analysis of serious post-marketing cases did not support a pattern or causal association due to presence of confounding factors or alternative explanations for the event". In contrast, the MAH concludes that "the current evidence suggests a reasonable causal association with the vaccine to confirm a safety signal".

Rapporteur assessment comment:

This conclusion of the MAH is unexpected, contradictory and not comprehensible – also in view of its conclusions drawn from the analyses of the signals diarrhoea and dyspnoea – and not really supported by the data presented. If tinnitus is considered part of an anxiety or stress reaction after vaccination, it does not necessarily need to be labelled as a separate adverse reaction but be added under the appropriate section. There is no discussion of possible pathophysiological mechanisms suggesting a link between vaccination and tinnitus. Further, causality analysis is missing.

Rapporteur assessment comment:

In Appendix 10 of the PBRER, section 1.4, p. 352, the MAH states that in O/E analyses, lower background rates were applied for myocarditis/pericarditis and for anaphylaxis in the 8th SSR than thereafter (myocarditis/pericarditis: 8th SSR 11.89/100,000 person-years, after review 21.88/100,000 person-years; anaphylaxis: 8th SSR 18.10/100,000 person-years, after review 56.67/100,000 person-years). This must be taken into account when comparing data over time. in addition, the MAH describes in Appendix 10 the sources of the background incidence rates used for the further O/E analyses.

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.

Signal evaluation reports on all other signals listed had been provided in previous safety reports and assessed in the respective documents.

In section 15.1.2.2.3, the term myocarditis should be replaced by pericarditis.

2.3. Evaluation of risks and safety topics under monitoring

The MAH states to closely monitor the following safety topics based on recommendations for COVID-19 vaccines or upon request from health authorities: anaphylaxis, autoimmune hepatitis, autoimmune thyroiditis, Bell's palsy, cerebral venous sinus thrombosis, chronic fatigue syndrome, encephalitis and encephalomyelitis, fibromyalgia, generalised convulsions, Guillain-Barré syndrome, haemorrhagic stroke, ischaemic stroke, multiple sclerosis, myocardial infarction, myocarditis and pericarditis, optic neuritis, postural orthostatic tachycardia syndrome, rheumatoid arthritis, spontaneous abortion, thrombocytopenia, and venous thromboembolism.

The MAH outlines some principles and limitations of its O/E analyses. Using predefined search strategies, it lists the number of ICSRs identified in the reporting interval and cumulatively, and presents O/E analyses when performed.

Autoimmune hepatitis: One ICSR was retrieved for the interval and cumulatively. The MAH did not identify a safety signal.

Autoimmune thyroiditis: The MAH's query of its global vaccine safety database retrieved two initial ICSRs for the interval and three ICSRs cumulatively. According to the MAH, no safety signal was identified.

Bell's palsy: Five ICSRs were retrieved for the interval, and 11 ICSRs cumulatively. A temporal relationship was present for most AEs. Results of O/E and sensitivity analyses showed lower than expected rates. The MAH did not identify a safety signal.

Cerebral venous sinus thrombosis: For the interval and cumulatively, a single ICSR was retrieved. The MAH did not identify a safety signal.

Chronic fatigue syndrome: For the interval and cumulatively, two ICSRs were retrieved. The MAH did not identify relevant safety information in these reports.

Fibromyalgia: The MAH's query retrieved no ICSRs for the interval and one ICSR cumulatively. No safety signal was identified.

Generalised convulsions: For the interval and cumulatively, the MAH's query retrieved seven and ten ICSRs, respectively. O/E analysis calculated using a risk window of 0-1 days showed that the observed rate was increased compared to the expected rate, but this increase was not statistically significant unless assuming 75% underreporting. No safety signal was identified.

Guillain-Barré syndrome: Three initial ICSRs were retrieved for the interval, and five ICSRs cumulatively. All five reports were assessed as level 4 Brighton Collaboration criteria due to insufficient clinical information. When assuming 75% underreporting, there was a statistically significant increase in the observed rate compared to the expected rate, with a RR of 5.55 (95% CI 1.80-12.96). The MAH did not identify a safety signal.

Haemorrhagic stroke: For the interval and cumulatively, ten ICSRs were retrieved which included ten AEs coded to the PT "cerebrovascular accident". No safety signal was identified.

Ischaemic stroke: The MAH's search identified 12 ICSRs for the interval, and 14 ICSRs cumulatively. The aforementioned ten ICSRs with AEs coded to the PT "cerebrovascular accident" are included here. The MAH did not identify a safety signal.

Multiple sclerosis: A single follow-up ICSR was retrieved for the interval, and three ICSRs were retrieved cumulatively. The MAH notes that overall, there was insufficient definitive evidence to establish a causal association, and that no safety signal was identified.

Myocardial infarction: The MAH's search identified 11 ICSRs for the interval, and 16 ICSRs cumulatively. No safety signal was identified.

Optic neuritis: For the interval and cumulatively, a single ICSR was retrieved. No safety signal was identified.

Postural orthostatic tachycardia syndrome: For the interval and cumulatively, two ICSRs were retrieved. The MAH did not identify a safety signal.

Rheumatoid arthritis: Two follow-up ICSR were retrieved for the interval, and three ICSRs were retrieved cumulatively. No safety signal was identified.

Spontaneous abortion: No ICSRs were retrieved for the interval, and four ICSRs were retrieved cumulatively. The MAH did not identify a safety signal.

Thrombocytopenia: Two follow-up ICSRs were retrieved for the interval, and five ICSRs cumulatively. The MAH did not identify any relevant safety information to establish a causal association.

Venous thromboembolism: For the interval and cumulatively, the MAH's query retrieved 12 and 19 ICSRs, respectively. No safety signal was identified.

Besides, the MAH queried its global vaccine safety database for the cumulative period up to 19 December 2022 for the following safety topics: death (all cause), pregnancy, vaccine anxiety-related reactions, cholecystitis, inflammatory eye disorders, menstrual disorders, paraesthesia, and reactogenicity profile (second dose and boosters, based on impurity levels).

Death, all cause: Using its prespecified search strategy, the MAH retrieved nine ICSRs (eight initial and one follow-up) for the interval and cumulatively. These included 23 AEs and the most frequently reported PTs with fatal outcome were "adverse event following immunisation" (n = 2), "cerebrovascular accident" (n = 2), "altered state of consciousness" (n = 1), "cardiac death" (n = 1), "cardiac disorder" (n = 1), "cardio-respiratory arrest" (n = 1), "chest discomfort" (n = 1), "concomitant disease aggravated" (n = 1), "death" (n = 1), and "decreased appetite" (n = 1). After the data lock point, the MAH received another fatal case which was included in the MAH's O/E analysis. According to the MAH, there was insufficient evidence to establish a causal association between death and Nuvaxovid. Results of O/E analyses showed lower than expected rates, and no safety signal was identified.

Vaccine anxiety-related reactions: 28 ICSRs were retrieved for the interval, and 48 ICSRs were retrieved cumulatively (5 males, 41 females, 2 individuals of unspecified sex). These 48 ICSRs included 48 AEs (4 serious and 44 non-serious) coded to the PTs "anxiety" (n = 36), "nervousness" (n = 6), "agitation" (n = 4), "stress" (n = 1), and "tension" (n = 1). The MAH did not identify a safety signal here.

Cholecystitis: For the interval and cumulatively, the MAH identified two and eight ICSRs, respectively. The eight AEs reported 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 did not identify a safety signal.

Inflammatory eye disorders: The MAH's query retrieved 26 ICSRs for the interval and 57 ICSRs cumulatively (11 males, 46 females). These 57 ICSRs included 64 AEs (10 serious and 54 non-serious) coded to the PTs "eye swelling" (n = 17), "ocular hyperaemia" (n = 7), "photophobia" (n = 6), "swelling of eyelid" (n = 5), "diplopia" (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 states that no safety signal was identified.

Herpes zoster: For the interval and cumulatively, 12 and 38 ICSRs were retrieved, respectively. These 38 ICSRs included 40 AEs (4 serious and 36 non-serious) coded to the PTs "herpes zoster" (n = 37), "herpes zoster oticus" (n = 1), "herpes zoster reactivation" (n = 1), and "ophthalmic herpes zoster" (n = 1). The MAH did not identify a safety signal.

Reactogenicity profile – second dose and boosters (based on impurity levels): For the interval and cumulatively, 35 and 111 ICSRs including 714 AEs (114 serious and 600 non-serious) were retrieved, respectively. The MAH states having reviewed the reports to identify any trend related to adverse events reported with specific batches. No trends related to reactogenicity based on impurity levels specifically after a second dose and/or a booster were identified.

Rapporteur assessment comment:

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

PBRER, p. 149, section 15.3.5 on herpes zoster: 9 males, 26 females, 3 females, and 3 individuals of

unspecified sex result in a total of 41 (not 38) individuals. Probably the extra listed 3 females have been included by mistake.

2.4. Characterisation of risks

In section 16 of its PBRER, the MAH provides updates on the important potential risk, vaccination failures, and missing information. No risks were not categorised as important.

On 01 September 2022, myocarditis and/or pericarditis was reclassified from an important potential risk to an important identified risk for Nuvaxovid in the core (EU) RMP. The EU SmPC variation to include myocarditis and pericarditis was approved on 25 October 2022.

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD): During the reporting interval and cumulatively, the MAH did not retrieve any ICSRs using its prespecified search strategy.

Vaccination failures, lack of efficacy: For the interval and cumulatively, six and seven ICSRs were retrieved, respectively. The MAH did not identify a safety signal.

Use in pregnancy and while breastfeeding: Regarding use in pregnancy, three initial ICSRs were retrieved for the interval and seven ICSRs cumulatively. According to the MAH, six ICSRs had pregnancy associated AEs which were coded to the PTs "abortion spontaneous" (n = 4) and "maternal exposure during pregnancy" (n = 2). Regarding use while breastfeeding, no ICSRs were retrieved for the interval and two ICSRs cumulatively. These two ICSRs included two AEs (both non-serious) coded to the PTs "lactation puerperal increased" (n = 1) and "suppressed lactation" (n = 1). According to the MAH, all reports of use in pregnancy and during breastfeeding did not raise any safety concerns.

Use in immunocompromised patients: For the interval and cumulatively, three and six ICSRs were retrieved, respectively. The MAH's review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders): 239 ICSRs were retrieved for the interval, and 467 ICSRs were retrieved cumulatively. These 467 ICSRs included 2,113 AEs (426 serious AEs, thereof 10 fatal, and 1,687 non-serious AEs), with the most frequently reported PTs "dizziness" (n = 57), "chest pain" (n = 47), "dyspnoea" (n = 42), "paraesthesia" (n = 40) and "tachycardia" (n = 34). The MAH's review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Use in patients with autoimmune or inflammatory disorders: For the interval and cumulatively, 66 and 166 ICSRs were retrieved, respectively. These 166 ICSRs included 855 AEs (186 serious AEs, thereof 8 fatal, and 669 non-serious AEs), with the most frequently reported PTs "headache" (n = 52) and "fatigue" (n = 37). The MAH's review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population.

Interaction with other vaccines: No ICSRs were retrieved for the interval, and one ICSR was retrieved cumulatively. However, in its assessment, the MAH found that this report did not meet the inclusion criteria.

Long-term safety: The MAH notes that long-term safety is evaluated by routine monitoring of PASSs. As no patients have been enrolled in the current PASSs, no new information determining long-term safety was identified.

The MAH does not propose any changes to the list of safety concerns. It notes that there are no additional risk minimisation measures in place for the vaccine.

Rapporteur assessment comment:
The safety concerns remain unchanged.

3. Benefit evaluation

There are no new data on efficacy that alters previous assessments, and which are described in the approved product information.

4. Benefit-risk balance

The MAH states that based on the cumulative safety data received from clinical trials and post-authorisation as of 19 December 2022 and with respect to the efficacy of Nuvaxovid in preventing COVID-19 caused by SARS-CoV-2, the overall benefit-risk balance of the vaccine remains positive.

The PRAC rapporteur agrees and 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>

Not applicable.

6. <MAH responses to Request for supplementary information>

Rapporteur assessment comment:

7. < Comments from Member States >

Member states' comments:
Endorsing comments from FR and BE.

PERIODIC BENEFIT-RISK EVALUATION REPORT

FOR

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

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-Jun-2022 to 19-Dec-2022

Date of Report: 13-Feb-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 second Periodic Benefit-Risk Evaluation Report (PBRER) for Nuvaxovid (SARS-CoV-2 recombinant, Spike Protein, adjuvanted; also referred to as NVX-CoV2373 interchangeably in the document) compiled for Health Authorities (HA) and 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. This report summarises the interval and cumulative safety data received by Novavax (hereafter referred to as NVX) for the interval covering 20-Jun-2022 to 19-Dec-2022.

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

Medicinal Product

NUVAXOVID is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2). NUVAXOVID is-authorised- as a two-dose primary series in individuals 12 years of age and older authorised as COVOVAX for individuals 7 years and older), and as a booster dose in adults. NUVAXOVID is a purified full-length SARS-CoV-2 recombinant spike (S) protein that is stabilised in its prefusion 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.

NUVAXOVID is a suspension 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 as a multi-dose vial of 10 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 the NUVAXOVID is two doses (0.5 mL each) given 3 weeks apart. A booster dose of NUVAXOVID (0.5 m/L) may be administered approximately 6 months after completion of the primary series. 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

NVX-CoV2373 is currently authorised as NUVAXOVID and COVOVAX in multiple regions for active immunisation to prevent COVID-19 caused by SARS-CoV-2 NUVAXOVID is authorised as a primary series for individuals over 12 years of age and as a booster dose for adults as noted in the table below. In India, COVOVAX is authorised as a primary series vaccine for individuals 7 years and older.

Trade Name (Active Pharmaceutical Ingredient)	Country	MA Type	Current Status	Authorisation Date	Partner Name / MAH
COVOVAX™ (NVXCoV2373)	Indonesia	EUA (Adult ≥ 18 years)	Authorised	31-Oct-2021	SIIPL
COVOVAX™ (NVXCoV2373)	Philippines	EUA (Adult ≥ 18 years)	Authorised	17-Nov-2021	SIIPL
COVOVAX™ (NVXCoV2373)	WHO	EUL (Adult ≥ 18 years)	Authorised	17-Dec-2021	SIIPL
NUVAXOVID™ (SARS-CoV-2 rS Protein Nanoparticle Vaccine [Recombinant]) (NVXCoV2373)	WHO	EUL (Adult ≥ 18 years)	Authorised	20-Dec-2021	Novavax Czech Republic (NVX CZ)
NUVAXOVID™ - COVID-19 Vaccine (recombinant, adjuvanted) (NVX-CoV2373)	EU	CMA (Adult ≥ 18 years)	Authorised	20-Dec-2021	NVX CZ
NUVAXOVID™ Dispersion for Injection (NVXCoV2373)	UAE	EUA (Adult ≥ 18 years)	Authorised	26-Dec-2021	GULF MED MEDICINES L.L.C.
COVOVAX™ (NVXCoV2373)	India	EUA (Adult ≥ 18 years)	Authorised	28-Dec-2021	SIIPL
NUVAXOVID Pre-filled Syringe (SARS-CoV-2 S Protein Vaccine (Recombinant) (NVXCoV2373)	South Korea	BLA (Adult ≥ 18 years)	Authorised	12-Jan-2022	SK Bioscience Co., Ltd.
NUVAXOVID™ (SARS-CoV-2 rS [NVX-CoV2373]) COVID-19 VACCINE adjuvanted suspension for injection vial	Australia	Provisional Registration (Adult ≥ 18 years)	Authorised	20-Jan-2022	Biocelect Pty Ltd.

Trade Name (Active Pharmaceutical Ingredient)	**Country**	**MA Type**	**Current Status**	**Authorisation Date**	**Partner Name / MAH**
NUVAXOVID™ COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) (NVXCoV2373)	UK	CMA (Adult ≥ 18 years)	Authorised	03-Feb-2022	NVX CZ
NUVAXOVID™ COVID-19 Vaccine (adjuvanted) Suspension for Injection 0.5ml / Vial (NVXCoV2373)	Singapore	Interim Authorisation (PSAR) (Adult ≥ 18 years)	Authorised	03-Feb-2022	PharmEng Technology Pte Ltd.
NUVAXOVID™ 10 µg/mL solution for Injection (NVXCoV2373)	New Zealand	Provisional Consent (Adult ≥ 18 years)	Authorised	04-Feb-2022	Biocelect New Zealand Ltd.
NUVAXOVID™ [COVID-19 Vaccine (NVX-COV2373)]	Canada	NDS (Adult ≥ 18 years)	Authorised	17-Feb-2022	NVX, Inc.
COVOVAX™ (NVXCoV2373)	Bangladesh	EUA (Adult ≥ 18 years)	Authorised	22-Feb-2022	SIIPL
COVOVAX™ (NVXCoV2373)	India	EUA (Adolescents ≥ 12 to < 18 years)	Authorised	09-Mar-2022	SIIPL
COVOVAX™ (NVXCoV2373)	Thailand	EUA (Adult ≥ 18 years)	Authorised	22-Mar-2022	SIIPL
NUVAXOVID™ 5ml Dispersion for Injection	Switzerland	CMA (Adult ≥ 18 years)	Authorised	12-Apr-2022	Future Health Pharma GmbH
NUVAXOVID™ Intramuscular Injection (SARS-CoV-2rS)	Japan	J-NDA (Primary and booster [homologous and heterologous])	Authorised	19-Apr-2022	Takeda
COVOVAX™ (NVXCoV2373)	Thailand	EUA (Adolescents ≥12 to <18 years)	Authorised	19-May-2022	SIIPL
NUVAXOVID (SARS-CoV-2 rS [NVX-CoV2373]) COVID-19 VACCINE adjuvanted suspension for injection vial	Australia	Provisional Registration (Booster)	Authorised	09-Jun-2022	Biocelect Pty Ltd.

Trade Name (Active Pharmaceutical Ingredient)	**Country**	**MA Type**	**Current Status**	**Authorisation Date**	**Partner Name / MAH**
NUVAXOVID™ 10 µg/mL solution for Injection (NVXCoV2373)	New Zealand	Provisional Consent (Heterologous and Homologous Booster)	Authorised	17-Jun-2022	Biocelect Pty Ltd.
NUVAXOVID™ Novavax COVID-19 Vaccine	Taiwan	EUA (Adult ≥ 18 years)	Authorised	22-Jun-2022	NVX, Inc.
COVOVAX™ (NVXCoV2373)	India	EUA (Age group ≥7 to <12 years)	Authorised	28-Jun-2022	SIIPL
NUVAXOVID™ - COVID-19 Vaccine (recombinant, adjuvanted) (NVX-CoV2373)	EU	CMA (Adolescents ≥12 and <18 years)	Authorised	01-Jul-2022	NVX CZ
NUVAXOVID™	Israel	Approval of Import under Regulation 29(a)(9)	Authorised	06-Jul-2022	Dor Pharmaceutical Services
Novavax COVID-19 Vaccine	USA	EUA (Adult ≥ 18 years)	Authorised	13-Jul-2022	NVX, Inc
NUVAXOVID™ Intramuscular Injection (SARS-CoV-2rS)	Japan	J-NDA (Adolescents ≥12 and < 18 years)	Authorised	21-Jul-2022	Takeda
NUVAXOVID (SARS-CoV-2 rS [NVX-CoV2373]) COVID-19 VACCINE adjuvanted suspension for injection vial	Australia	Provisional Registration (Adolescents ≥12 and < 18 years)	Authorised	22-Jul-2022	Biocelect Pty Ltd.
NUVAXOVID Pre-filled Syringe (SARS-CoV-2 S Protein Vaccine (Recombinant)) (NVXCoV2373)	South Korea	BLA (Adolescents ≥12 and < 18 years of age)	Authorised	12-Aug-2022	SK Bioscience Co., Ltd.
COVOVAX™ (NVXCoV2373)	South Africa	EUA (Adult ≥ 18 years)	Authorised	16-Aug-2022	SIIPL
NUVAXOVID™ 10 µg/mL solution for Injection (NVXCoV2373)	New Zealand	Provisional Consent (Adolescents ≥12 and < 18 years)	Authorised	18-Aug-2022	Biocelect Pty Ltd.

Trade Name (Active Pharmaceutical Ingredient)	**Country**	**MA Type**	**Current Status**	**Authorisation Date**	**Partner Name / MAH**
Novavax COVID-19 Vaccine	USA	EUA (Adolescents ≥12 and < 18 years)	Authorised	19-Aug-2022	NVX, Inc.
NUVAXOVID™ COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) (NVXCoV2373)	UK	CMA (Adolescents ≥12 and < 18 years)	Authorised	26-Aug-2022	NVX CZ
NUVAXOVID™ Novavax COVID-19 Vaccine	Taiwan	EUA (Adolescents ≥12 and < 18 years)	Authorised	31-Aug-2022	NVX, Inc.
NUVAXOVID™ 5ml Dispersion for Injection	Switzerland	CMA (Adolescents ≥12 and < 18 years) and Booster for adults >18 years	Authorised	02-Sep-2022	Future Health Pharma GmbH
NUVAXOVID™ - COVID-19 Vaccine (recombinant, adjuvanted) (NVX-CoV2373)	EU	CMA (Heterologous and homologous booster for adults)	Authorised	06-Sep-2022	NVX CZ
Novavax COVID-19 Vaccine	USA	EUA (Booster for ≥ 18 years)	Authorised	19-Oct-2022	NVX, Inc.
NUVAXOVID™ COVID-19 Vaccine (SARS-CoV-2 rS with Matrix-M1 Adjuvant) (NVXCoV2373)	UK	CMA (Adult booster)	Authorised	09-Nov-2022	NVX CZ
NUVAXOVID™ [COVID-19 Vaccine (NVX-COV2373)]	Canada	NDS (Adult homologous booster)	Authorised	17-Nov-2022	NVX, Inc.
NUVAXOVID™ (SARS-CoV-2 rS Protein Nanoparticle Vaccine [Recombinant]) (NVXCoV2373)	WHO	EUL (Adolescents ≥12 and < 18 years)	Authorised	17-Nov-2022	NVX CZ
NUVAXOVID™ (SARS-CoV-2 rS Protein Nanoparticle Vaccine [Recombinant]) (NVXCoV2373)	WHO	EUL (Adult booster)	Authorised	17-Nov-2022	NVX CZ

Trade Name (Active Pharmaceutical Ingredient)	Country	MA Type	Current Status	Authorisation Date	Partner Name / MAH
NUVAXOVID™ [COVID-19 Vaccine (NVX-COV2373)]	Canada	NDS (Adolescents ≥12 and < 18 years)	Authorised	06-Dec-2022	NVX, Inc.

Changes to Reference Safety Information

The NUVAXOVID Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the Company Core Data Sheet (CCDS) Version (V) 3.0, effective date 03-May-2022.

During the reporting interval, the CCDS was updated three times to versions 4.0 (effective date 27-Jun-2022), 5.0 (effective date 21-Jul-2022) and 6.0, (effective date 10-Aug-2022). Version 6.0 was used to assess expectedness of reported adverse events.

Summary of Clinical Trials

The below table provides an overview of number of ongoing clinical trials (CTs) during the reporting interval for NVX-CoV-2373.

Study population	Summary of Ongoing Studies
Adults	2019nCoV-101 (Part 2), 2019nCoV-301, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311, 2019nCoV-501, and 2019nCoV-505
Adolescents	2019nCoV-301 adolescent sub-study
Paediatrics	2019nCoV-503

During the reporting interval, 2019nCoV-ICC-E-101 study was completed for the evaluation of safety and immunogenicity of combination therapy (quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy subjects ≥ 50 to ≤ 70 years.

Clinical Trial Exposure

Cumulatively, 46,171 subjects have received at least one dose of NVX-CoV2373 during ongoing and completed clinical trials.

Post-Authorisation Exposure

During the reporting interval, 1,338,871 NVX-CoV2373 doses (1,311,523 NUVAXOVID and 27,348 COVAVAX) were administered and 63,765,380 doses (54,436,730 NUVAXOVID and 9,328,650 COVOVAX) were distributed globally.

Cumulatively, 2,393,247 NVX-CoV2373 doses (2,365,899 NUVAXOVID and 27,348 COVOVAX) were administered and 103,799,960 NVX-CoV2373 doses (94,471,310 NUVAXOVID and 9,328,650 COVOVAX doses) were distributed globally.

Overview of Individual Case Safety Reports

A total 1,363 spontaneous ICSRs were received during the 6-month reporting interval (of which 69 ICSRs contained follow-ups), with 4,950 adverse events (AEs) (755 serious unlisted AEs, 259 serious listed AEs, 2,222 non-serious unlisted AEs, and 1,714 non-serious listed AEs). A total of 9 (8 initial and 1 follow-up) fatal ICSRs were reported during the 6-month interval.

Cumulatively, 3,161 spontaneous ICSRs have been received (of which 663 were follow-ups), reporting 12,430 AEs (1,402 serious unlisted AEs, 525 serious listed AEs, 5,845 non-serious unlisted AEs, and 4,658 non-serious listed AEs). A total of 9 fatal ICSRs have been reported cumulatively.

Routine Monitoring

Qualitative and quantitative methods are employed for surveillance across interval and cumulative data for any unexpected, potential Adverse Events Following Immunisation (AEFI) and for the analysis of pre-specified AESIs and additional safety topics described below.

AESI

Pre-specified AESIs are under routine surveillance for the pandemic setting. Signal generation methods include observed-to-expected (O/E) analyses. The global vaccine safety database is routinely queried across cumulative data for the safety topics listed below according to pre-specified search strategies. All ICSRs retrieved are reviewed individually and in aggregate, and O/E analyses is routinely performed. Cumulative O/E analyses were performed up to the Datal Lock Point, 19-Dec-2022).

- 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
- 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

- Haemorrhagic Stroke
- Ischaemic Stroke
- Kawasaki's Disease
- Major Congenital Anomalies
- Maternal Death
- Microcephaly
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Stillbirth
- Sudden Death
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Transverse Myelitis
- Vaccine-Associated Enhanced Disease
- Venous Thromboembolism

Other Safety Topics

Other pre-specified safety topics under routine surveillance include:

- Fatal reports
- Vaccine anxiety-related reactions
- Cholecystitis
- Inflammatory eye disorders
- Herpes zoster
- Menstrual disorders
- Paraesthesia
- Reactogenicity profile - second dose and boosters (based on impurity levels)

Overview of Signals: New, Ongoing, or Closed

Cumulatively, validated signals of anaphylaxis, paraesthesia/hypoaesthesia, myocarditis and pericarditis 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 and acute coronary syndrome associated with an allergic reaction have been refuted and closed. These topics will continue to be monitored per routine surveillance.

During the reporting interval, new signals of diarrhoea, dyspnoea and tinnitus were validated upon receipt of queries from the Pharmacovigilance Risk Assessment Committee (PRAC) following preliminary assessment of the first Periodic Benefit Risk Evaluation Report (PBRER), and signal evaluations have been completed. The signals of diarrhoea and dyspnoea were refuted and the signal for tinnitus has been confirmed.

Summary Evaluation of Important Risks and New Information

During the reporting interval myocarditis and/or pericarditis was updated to an important identified risk for NVX-CoV2373.

Overall Benefit-Risk Analysis Evaluation

Based on interim analysis from 2 pivotal Phase III CTs, NVX-CoV2373 demonstrated high levels of efficacy in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to SARS-CoV-2 with onset from at least 7 days after second vaccination in serologically negative adult and adolescent subjects. No subject in the NVX-CoV2373 study arm had PCR-confirmed symptomatic moderate or severe COVID-19 requiring hospitalisation, ICU admission, or mechanical ventilation with onset from at least 7 days after second vaccination following initial analysis. In both pivotal Phase III studies, the frequency of Grade 3 solicited local and systemic TEAEs were low but inclined to occur at a higher frequency in the NVX-CoV2373 group than in the placebo group. In both studies, very few subjects reported Grade 4 solicited local and systemic TEAEs.

The benefits of NUVAXOVID have been established across the clinical development program and remain unchanged from the date of first marketing authorisation as reflected in the current global labelling.

For the cumulative period up to 19-Dec-2022, signals of anaphylaxis and paraesthesia/hypoaesthesia have been confirmed and the CCDS has been updated to include anaphylaxis in the current general warning and precautions and paraesthesia/hypoaesthesia 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).

On 01-Sep-2022, the core (EU) RMP was updated to reclassify myocarditis and/or pericarditis from an important potential risk to an important identified risk.

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.

Conclusion

During the reporting interval, NVX has received additional authorisations for adults, adolescents, homologous and heterologous booster indications. Anaphylaxis, myocarditis and pericarditis were added to special warnings and precautions and paraesthesia/hypoaesthesia were added as undesirable side effects in the CCDS along with updates to the core RMP, IB and SmPC, in accordance with specified timelines.

The signals of diarrhoea, dyspnoea, syncope, menstrual disorders, tachycardia with other rhythm abnormalities, have been refuted and Signal Evaluation Reports (SERs) have been appended to this report.

The signal of tinnitus was confirmed and an update to CCDS is planned.

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

The overall benefit-risk profile of NVX-CoV2373 remains positive.

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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
ACS	Acute Coronary Syndrome
ACIP	Advisory Committee on Immunisation Practices
ADR	Adverse Drug Reaction(s)
AEFI	Adverse Event Following Immunisation
AESI	Adverse Event(s) of Special Interest
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
Anti-N	Antinuclear capsid protein
AR	Adverse Reaction(s)
ARGUS	Analytical Reports Gathering and Updating System
ATAGI	Australian Technical Advisory Group on Immunisation
AV	Atrioventricular
BALB/c	Albino Immunodeficient Laboratory-Bred Strain of Mouse
BC	Brighton Collaboration
BEST	Biologics Effectiveness and Safety
BFARM	Federal Institute for Drugs and Medical Devices
BLA	Biologics License Application
BNT	BNT162b2 Pfizer–BioNTech
BP	Blood Pressure
CBER	Centre For Biologics Evaluation and Research
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CFS	Chronic Fatigue Syndrome
ChAd	ChAdOx1 nCoV-19, AstraZeneca
CI	Confidence Interval
CIOMS	Council for International Organisation of Medical Sciences
CMA	Conditional Marketing Authorisation
CMI	Cell Mediated Immunity
CMQ	Customised MedDRA Query
COPD	Chronic Obstructive Pulmonary Disease
COVID 19	Coronavirus disease
CPRD-GOLD	Clinical Practice Research Datalink
CSF	Cerebrospinal Fluid

Acronym	Abbreviation Definition
CSR	Clinical Study Report
CT	Clinical Trial(s)
CTLA-4	Cytotoxic T-Lymphocyte Associated protein 4
CXR	Chest X-Ray
DAEN	Database of Adverse Event Notifications
DIBD	Development International Birth Date
DLP	Data Lock Point
DME	Designated Medical Event
DNA	Deoxy ribonucleic acid
ECDC	European Center for Disease Prevention and Control
ECG	Electrocardiogram
ED	Emergency Department
EMA	European Medicines Agency
EoS	End of Study
ER	Emergency Room
eRMR	electronic Reaction Monitoring Report
EU	European Union
EU SmPC	European Summary of Product Characteristics
EUA	Emergency Use Authorisation
EUL	Emergency Use Listing
EU-RMP	European Risk Management Plan
EVDAS	EudraVigilance Data Analysis System
GBS	Guillain-Barré Syndrome
GLP	Good Laboratory Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HCW	Healthcare Worker
HGLT	High Level Group Term
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HZ	Herpes Zoster
IB	Investigator's Brochure
IBD	International Birth Date
ICC	Influenza COVID Combination
ICD	International Classification of Disease
ICH	International Conference on Harmonisation

Acronym	Abbreviation Definition
ICSR	Individual Case Study Report
ICU	Intensive Care Unit
IDI	Integrated Data Infrastructure
IgG	Immunoglobulin G
IFN γ	Interferon Gamma
IL-2	Interleukin-2
IM	Intramuscular(ly)
IME	Important Medical Event
IR	Incidence Rate
J-NDA	Japanese New Drug Application
KCDC	Korea Centre for Disease Control and Prevention
KD	Kawasaki's disease
LBCI	Lower Bound Confidence Interval
LL	Line Listing
LLT	Lowest Level Term(s)
LP	License Partner
LT	Life Threatening
m1273	mRNA-1273, Moderna
MA	Marketing Authorisation
MAAE	Medically Attended Adverse Event(s)
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFR	Manufacturer
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
mL	Milliliter(s)
mmHg	Millimeter of Mercury
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
MVD	Medical Data Vision Co. Ltd (MVD)
NA or N/A	Not Available or Not Applicable
NDS	New Drug Submission
nAb	Neutralising antibody titers
NHC	National Hauora Coalition
NMDS	National Minimum Data Set
No.	Number
NSAIDs	Non-steroidal Anti-inflammatory Drugs

Acronym	Abbreviation Definition
NSL	Non-Serious Listed
NTD	N-terminal domain
NVX	Novavax, Inc.
NVX, CZ	Novavax, Czech Republic
NZ MoH	New Zealand Ministry of Health
O/E	Observed vs Expected
OUHSC	University of Oklahoma Health Sciences Center
PASS	Post Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PD	peptidase domain
PEI	Paul Ehrlich Institute
pH	Potential of Hydrogen
PIMMC	Potential Immune-Mediated Medical Conditions
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)
PubMed	Public/Publisher Medline
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement(s)
PVP	pharmacovigilance plan
PY	Person years
qNIV	Quadrivalent Nanoparticle Influenza Vaccine
RBD	Receptor-binding domain
RoB2	Risk of Bias Tool
ROR	Reporting Odds Ratio
Rr	Reporting Rate
RR	Rate Ratio
RSI	Reference Safety Information
RT-PCR	reverse transcription-polymerase chain reaction
S	Spike
SAE	Serious Adverse Event(s)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SCR	Seroconversion rate
SER	Signal Evaluation Review

Acronym	**Abbreviation Definition**
SIIPL / SII	Serum Institute of India PVT. LTD.
SL	Serious Listed
SMC	Signal Management Committee
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPEAC	Safety Platform for Emergency vACcines
SRT	Safety Review Team
SSR	Summary Safety Report
ST	Summary Tabulation(s)
SUL	Serious Unlisted
TEAE	Treatment Emergent Adverse Event
TGA	Therapeutic Goods Administration
TTO	Time to Onset
TNF α	Tumor Necrosis Factor Alpha
UAE	United Arab Emirates
UK	United Kingdom
UL	Unlisted
UMSOM	University of Maryland school of medicine
USA FDA	United States of America Food and Drug Administration
USG	United States Government
V	Version
VAC4EU	Vaccine monitoring Collaboration for Europe
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VBM	Variant Being Monitored
VE	Vaccine Efficacy
VOC	Variant of Concern
VOI	Variant of Interest
VS	Versus
VTE	Venous Thromboembolism
WHO	World Health Organisation
WOCBA	Women of Child-Bearing Age
WWMA	Worldwide Marketing Authorisation

1 INTRODUCTION

This is the second Periodic Benefit-Risk Evaluation Report (PBRER) for NVX-CoV2373 Coronavirus Disease (COVID-19) Vaccine (recombinant, adjuvanted) (SARS-CoV-2 rS also referred to as NVX-CoV2373 interchangeably in the document) compiled for Health Authorities (HA) which follows the International Conference on Harmonisation (ICH) E2C_Harmonised Tripartite Guideline PBRER; European Medicines Agency (EMA) E2C guideline on periodic benefit-risk evaluation report (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. This report summarises the interval and cumulative data received by Novavax (hereafter referred to as NVX in this report) global vaccine safety database from worldwide sources for the period covering 20-Jun-2022 to 19-Dec-2022.

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

NUVAXOVID is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). NUVAXOVID is authorised as a two-dose primary series in individuals 12 years of age and older (authorised as COVOVAX for individuals 7 years and older), and as a booster dose in adults. NUVAXOVID is a purified full-length SARS-CoV-2 recombinant spike (S) 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.

NUVAXOVID is a suspension for intramuscular injection. One dose (0.5 milliliters [mL]) of NUVAXOVID contains 5 micrograms (µg) of the SARS-CoV-2 S 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 in a multidose container of 10 doses of 0.5 mL each. The dispersion is colorless to slightly yellow, clear to mildly opalescent with a pH of 7.2.

The primary series of the 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.

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.

2 WORLDWIDE MARKETING AUTHORISATION STATUS

NVX-CoV2373 is currently authorised as NUVAXOVID and COVOVAX in multiple regions for active immunisation to prevent COVID-19 caused by SARS-CoV-2. NUVAXOVID is authorised as a primary series for individuals over 12 years of age and as a booster dose for adults. In India, COVOVAX is 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 (UAE), Dor Pharmaceutical Services (Israel) and Serum Institute of India Pvt Ltd. (SIIPL), (Bangladesh, India, Indonesia, Philippines, South Africa, Thailand and World Health Organisation [WHO]) Refer to Appendix 3, Table 29 for the WWMA Status.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting interval, there were no actions taken for safety reasons.

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) 3.0, effective date 03-May-2022 (refer to Appendix 2).

During the reporting interval, RSI was updated following confirmation of signals for anaphylaxis, myocarditis and/or pericarditis, paraesthesia and hypoaesthesia.

4.1 Safety Variations

The following safety variation procedures were approved based on Pharmacovigilance Risk Assessment Committee (PRAC) recommendations during the reporting interval.

- A type II safety variation was approved on 06-Sep-2022 and product information was updated based on confirmed signals of anaphylaxis, paraesthesia and hypoaesthesia.
- A type II safety variation was approved on 25-Oct-2022 and product information was updated based on confirmed signals of myocarditis and pericarditis.

4.2 Company Core Data Sheet (CCDS)

During the reporting interval, CCDS had three version updates to include the adolescent indication and the homologous booster dose following two-dose primary series respectively.

The current version of CCDS in effect, at the end of reporting interval is V6.0, effective date 10-Aug-2022 and was used to assess individual case safety reports (ICSRs) in the global vaccine safety database for listedness assessment (refer to Appendix 1). A summary of changes between the versions is presented in Table 1 below.

Table 1: CCDS Summary of Changes

Version number	Approval date	Summary of Changes
V3.0	03-May-2022	Section 4.2 Posology and Administration 1. Added subheading for "Primary series" to distinguish between primary series and booster dosing, for clarity. 2. booster dose of Novavax COVID-19 Vaccine (recombinant, adjuvanted) may be administered intramuscularly approximately 6 months after completion of the second dose in the primary series in individuals 18 years of age and older. Section 4.8 Undesirable Side Effects Added subheading to clarify "Primary series" before the associated text with a brief description of the studies and supporting data for administration of a booster dose. For each age group sub-heading under the Undesirable Effects section, "after two-dose primary series" has been after the age category name in the subsection headings for clarity Added NEW subheading for "subjects 18 years of age and older–after booster" with new text containing clinical study descriptions and supporting clinical study safety data for a booster dose of Novavax COVID-19 Vaccine, Adjuvanted from Study 2019nCoV-101 (Part 2) and Study 2019nCov-501
V4.0	27-Jun-2022	Section 4.8 Undesirable Effects Deleted injection site swelling (19%) and injection site redness (17%) under subheading Adolescents 12 through 17 years of age–after two-dose primary series to align with updated data of an Erratum to the pediatric expansion interim CSR from study 2019nCoV-301 approved on 29-Apr-2022 with the table 14.3.2.3.6 Summary of Solicited Reactions by Maximum Toxicity Grade Among Grades 1 or Higher 7 Days Following Any Vaccination Safety Analysis Set.
V5.0	21-Jul-2022	Section 4.4: Special Warnings and Precautions Updated sub-section 4.1.1 Hypersensitivity and anaphylaxis to amend the sentence to "Events of anaphylaxis have been seen with Novavax COVID-19 Vaccine (Recombinant, Adjuvanted)." Section 4.8 Undesirable Effects Updated to add sub-section post-marketing experience and Table (2) for post-marketing events. anaphylaxis as an immune system disorder, and hypoaesthesia and paraesthesia as nervous system disorders, with unknown frequency, are added to Table 2.
V 6.0	10-Aug-2022	Section 4.4 and Section 4.8 were updated to include Myocarditis and Pericarditis. Section 6.3 was updated to reflect extended in-use duration from 6 -12 hours post needle puncture.

5 ESTIMATED EXPOSURE AND USE PATTERNS

The cumulative number of subjects from ongoing and completed clinical trials (CTs) exposed to NVX-CoV2373, placebo and/or active comparator during the clinical development are summarised in Section 5.1 The estimates are based on actual exposure data from completed CTs and on enrolment/randomisation schemes from ongoing CTs.

Cumulatively, 46,171 subjects have received at least one dose of NVX-CoV2373 in the clinical development program as of the data lock point (DLP).

5.1 Cumulative Subject Exposure in Clinical Trials

Table 2 and Table 3 present estimates of cumulative number of subjects exposed to the NVX-CoV2373 from ongoing and completed CTs, from Development International Birth Date (DIBD) to the DLP of this PBRER.

Table 2: Estimated Cumulative Exposure in Adult Subjects

Treatment	Estimated Total Number of Subjects Exposed (> 18 years of age)[a]
NVX-CoV2373	43,839
Placebo (normal saline)	8,386
ICC (qNIV + NVX-CoV2373)	558
NVX-CoV2515	317
NVX-CoV2373+ NVX-CoV2515	317

a: Includes final study data from 2019nCoV-101 (Part1), 2019nCoV-101 (Part2), 2019nCoV-301 Adult, 2019nCoV-302, 2019nCoV-307, 2019nCoV-311, 2019nCoV-501, 2019nCoV-505 and 2019nCoV-ICC-E-101.

Table 3: Estimated Cumulative Exposure in Paediatric and Adolescent Subjects

Age group	Treatment[a]	
	NVX-CoV2373	Placebo
≥ 6 months to < 12 years	**180**	**100**
≥ 12 years to < 18 years (inclusive)	2,152	80

a: Includes data from 2019nCoV-301, adolescent sub-study and 2019nCoV-503 study.

Table 4 and Table 5 below present cumulative summary tabulations from completed CTs presented by age, sex, and racial/ethnic group.

Table 4: Cumulative Subject Exposure to NVX-CoV2373 from Completed CTs by Age and Sex

Age Range	Male	Female	Total
Adults (≥ 18 Years)	55	53	108

Includes data from final CSR for 2019nCoV-101 (Part 1)

Table 5: Cumulative Subject Exposure to NVX-CoV2373 from Completed CTs by Racial/Ethnic Group

Racial group	Number of Subjects
American Indian or Alaska Native	6
Asian	15
Black of African American	2
Native Hawaiian or Other Pacific Islander	1
White	84
Multiple	0
Total	108

Includes data from final CSR for 2019nCoV-101 (Part 1)

5.2 Interval and Cumulative Estimated Exposure Data from Post-Authorisation Experience

The regional sources of administration and distribution data, including cut-off dates, are presented in Table 6. The demographic data available from each country is summarised in Table 7 below.

Administration data stratified by dose number and age group are provided in Table 8 and Table 9 respectively. Administration and Distribution of NUVAXOVID and COVOVAX by Country/Region are presented in Table 10.

During the reporting interval, 1,338,871 NVX-CoV2373 doses were administered in Australia, Canada, EU, India, Israel, Japan, New Zealand, Singapore, Switzerland, South Korea, Taiwan and USA and 63,765,380 doses (54,436,730 NUVAXOVID and 9,328,650 COVOVAX) were distributed globally (refer to Table 10 for administration and distribution data for the reporting interval).

Cumulatively, as of 19-Dec-2022, approximately 2,393,247 NVX-CoV2373 doses were administered in Australia, Canada, EU, India, Israel, Japan, New Zealand, Singapore, Switzerland, South Korea, Taiwan and USA and 103,799,960 NVX-CoV2373 doses (94,471,310 NUVAXOVID and 9,328,650 COVOVAX doses) were distributed globally (refer to Table 10 for cumulative administration and distribution data).

Table 6: Administration and Distribution of NUVAXOVID and COVOVAX Source Data by Country or Region

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]	Therapeutic Goods Administration via direct communications with COVID19VaccineData@Health.gov.au	14-Dec-2022	Novavax Global Sales	16-Dec-2022
Canada [a]	Public Health Agency of Canada (PHAC 2021)	19-Dec-2022 [c]	Novavax Global Sales	16-Dec-2022
EU [a]	European Center for Disease Prevention and Control ECDC 2022	19-Dec-2022 [c]	Novavax Global Sales	16-Dec-2022
Japan [a]	Takeda Pharmaceutical Company	18-Dec-2022	Takeda Pharmaceutical Company	18-Dec-2022
New Zealand (NZ) [a]	NZ (MoH) provided by (LP), Biocelect, via Biointelect	30-Nov -2022	Novavax Global Sales	16-Dec-2022
Singapore [a]	Singapore Health Sciences Authority HSAS 2022	31-Aug2022	Novavax Global Sales	16-Dec-2022
Switzerland [a]	Swiss Federal Office of Public Health (FOPH 2022)	19-Dec-2022	Novavax Distribution Department	16-Dec-2022
Taiwan [a]	Taiwan Centers for Disease Control (TCDC 2022)	19-Dec-2022	Novavax Global Sales	16-Dec-2022
USA [a]	US Centers for Disease Control and Prevention (CDC 2022)	19-Dec-2022 [c]	Novavax Global Sales	16-Dec-2022
Countries Not Included in O/E Analysis				
Bangladesh [b]	Ministry of Health and Family Welfare, Government of People's Republic of Bangladesh (MHFWGPRB 2023)	N/A	SIIPL	30-Nov-2022

Table 6: Administration and Distribution of NUVAXOVID and COVOVAX Source Data by Country or Region

Country	Administration Data Source	Administration Data Cut-Off Date	Distribution Data Source	Distribution Data Cut-off Date
India [b]	Government of India Ministry of Health and Family Welfare (Makino 2019 Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, Aoyama Y, Yanagawa H. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. Pediatrics International. 2019 Apr;61(4):397-403 MHFWGI 2022)	19-Dec-2022	SIIPL	30-Nov-2022
Indonesia [b]	N/A	N/A	SIIPL	30-Nov-2022
Israel [a]	Israeli Ministry of Health, via direct communication	07-Nov-2022	Novavax Global Sales	16-Dec-2022
Philippines [b]	Republic of the Philippines Department of Health Food and Drug Administration [RPFDA 2022]	N/A	SIIPL	30-Nov-2022
South Africa	N/A	N/A	SIIPL	30-Nov-2022
South Korea [a]	Korea Centers for Disease Control (KDCA) via Daily Inoculation Status Dashboard and COVID-19 Vaccine Weekly Safety Report (KDCA 2022)	04-Dec-2022	SK Bio Distribution Data	04-Dec-2022
Thailand [b]	N/A	N/A	SIIPL	30-Nov-2022
UAE [a]	N/A	N/A	Novavax Global Sales	N/A
UK [a]	UK Department of Health and Social Care, Vaccine Delivery Team via direct communications	N/A	Novavax Global Sales	16-Dec-2022

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

Table 8 below provides detailed information for the actual doses administered, doses estimated to have been administered based on distribution data (if applicable), and the total estimated number of doses administered by dose and presented for interval and cumulative period. Actual doses administered are included in Table 8 Column "Total Estimated Doses Administered" (i.e.,

Australia, Canada, EU, Japan, New Zealand, Singapore, Switzerland, Taiwan, India, Israel, South Korea and USA). A brief description of each column in Table 8 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 NUVAXOVID 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 from distribution data include the assumed number of doses administered as derived from distribution data. During the reporting interval, this method of re-distribution did not apply to any country. The method of calculation used for this redistribution 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 (from distribution data)". The cumulative data in the column: Total Estimated Doses Administered were the exposure values used in the O/E analyses. Exposure data were not included in the O/E analysis for countries from which no ICSRs have been reported. South Korean exposure data was excluded from the denominator of O/E to reduce the possibility of immortal time-bias related to incomplete data received from this country.

Available demographic data for each country or region based on available exposure data, are summarised in Table 7.

Table 7: Demographic Data (Sex and Age) Available by Country or Region

Country/ Region	Sex Data Available (Y/N)	Age Data Available (Y/N)	Format of Age Data
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
United States	N	N	NA

Table 7: Demographic Data (Sex and Age) Available by Country or Region

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

Where provided (Australia, the EU, New Zealand, Japan and Switzerland) administration data stratified by age groups is presented in Table 9. No extrapolations were made. 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 < 18 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.

Table 8: Interval and Cumulative Estimated Exposure Data (Administered) from Post-Authorisation Experience

Dose	Actual Doses Administered [a]	Adjusted doses including re-allocated doses [b]	Calculated Doses Administered [c]	Total Estimated Doses Administered [d]
Interval				
First Dose	142,981	151,411	6,601	158,012
Second Dose	132,115	139,998	6,601	146,599
Booster Dose	1,060,969	1,064,748	8,800	1,073,548
Unknown Dose Number	16	0	0	0
Interval Total	1,338,871	1,358,947	22,002	1,380,949
Cumulative				
First Dose	514,707	552,324	6,601	558,925
Second Dose	382,518	405,648	6,601	412,249
Booster Dose	1,493,059	1,498,787	8,800	1,507,587
Unknown Dose Number	19	0	0	0
Cumulative Total [e]	2,393,247	2,459,703	22,002	2,481,705

[a] Data presented as recorded. No assumptions or adjustments were made regarding this data. All countries with administration data are presented in this column. Refer to list of countries with administration data.

[b] Column represents administration data re-allocated to first and second dose only (refer to calculations above Table 8 this is used for calculating total estimated administration doses for O/E analysis). All countries with administration data are presented in this column. For a list of countries for which this re-allocation was applied, refer to text above Table 8

[c] Column represents administration data derived from distribution data. This was only done for Singapore. Assumptions applied to derive administered doses from distribution data are presented in Appendix 10.

[d] Column represents all estimated administration doses utilised in the O/E analysis. This column is a summation of columns b and c. All countries with either administration data or distribution 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

Table 9: Interval and Cumulative Actual Exposure Data (Administered) by Age Group from Post-Authorisation Experience

Total Doses Actually Administered [a,b,c]			
Dose	**Paediatrics**	**Adults**	**Elderly**
Interval			
First Dose	59	11,101	6,493
Second Dose	60	13,587	7,175
Third/Booster Dose	80	63,339	24,065
Interval Total	199	88,027	37,733
Cumulative			
First Dose	152	152,814	21,000
Second Dose	123	111,294	16,607
Third/Booster Dose	145	115,779	39,489
Cumulative Total	420	379,887	77,096

Note: Data Sources and cut-off dates are presented in Table 6.

[a] Data presented as recorded. The list of countries that included age data within the available administration data are presented in the text above.

[b] Some countries in the EU (Table 7) did not provide age categories consistently as per 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.

Table 10: Interval and Cumulative Exposure Data (Distributed and Administered) from Post-Authorisation Experience Presented by Region/LP

Region / LP	**Total Doses Administered** [a]	**Total Doses Distributed** [a]
Interval		
Australia (Biocelect Pty Ltd) [b]	78,953	14,371,700
Canada (NVX) [b]	4,071	6,485,900
EU (NVX) [b]	38,999	20,466,860
India (SIIPL) [c]	27,348	120,650
Indonesia (SIIPL) [c]	NA	9,008,000
Israel (Medicalix/Freyr) [b]	5	1,000,000
Japan (Takeda) [b]	251,404	4,597,210
New Zealand (Biocelect New Zealand Ltd.) [b]	3,135	756,000
Singapore (PharmaEng Technology Pte Ltd) [b]	18,073	111,000
South Korea (SK Bioscience) [b]	345,993	901,760
Switzerland (NVX) [b]	2,426	502,000
Taiwan (NVX) [b]	502,493	1,008,000
Thailand (SIIPL) [c]	Not available	200,000
UK (NVX) [b]	Not available	1,000,000
USA (NVX) [b]	65,971	3,236,300

Table 10: Interval and Cumulative Exposure Data (Distributed and Administered) from Post-Authorisation Experience Presented by Region/LP

Region / LP	Total Doses Administered [a]	Total Doses Distributed [a]
Interval Total	1,338,871	63,765,380
Interval Total Covovax	27,348	9,328,650
Interval Total Nuvaxovid	1,311,523	54,436,730
Cumulative		
Australia (Biocelect Pty Ltd.) [b]	235,549	21,236,300
Canada (NVX) [b]	11,087	9,724,000
EU (NVX) [b]	345,231	42,946,850
India (SIIPL) [c]	27,348	120,650
Indonesia (SIIPL) [c]	Not Available	9,008,000
Israel (Medicalix/Freyr) [b]	5	1,000,000
Japan (Takeda) [b]	269,922	8,238,590
New Zealand (Biocelect New Zealand Ltd.) [b]	7,039	2,031,800
Singapore (PharmaEng Technology Pte Ltd) [b]	18,073	615,000
South Korea (SK Bioscience) [b]	908,103	2,932,470
Switzerland (NVX) [b]	2,426	502,000
Taiwan (NVX) [b]	502,493	1,008,000
Thailand (SIIPL) [c]	Not Available	200,000
UK (NVX) [b]	Not Available	1,000,000
USA (NVX) [b]	65,971	3,236,300
Cumulative Total	2,393,247	103,799,960
Cumulative Total Covovax	27,348	9,328,650
Cumulative Total Nuvaxovid	2,365,899	94,471,310

[a] Data presented as recorded.
[b] NUVAXOVID
[c] COVOVAX

6 DATA IN SUMMARY TABULATIONS

The safety data includes summary tabulations of serious adverse events (SAEs) from CTs and spontaneous serious and non-serious adverse reactions from post-authorisation phase.

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA), V 25.1 was used for the coding of serious adverse events (SAEs) in clinical studies.

ADRs received following authorisation were coded using MedDRA V 25.0, at the beginning of the reporting interval and V25.1 at the end of reporting interval.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 4 presents cumulative summary tabulations of serious adverse events (SAEs from NVX-sponsored interventional Clinical Trials CTs, from the DIBD to the DLP of the PBRER. Data are extracted from the NVX global safety database and may contain unblinded information. Unblinded data may originate from completed CTs (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 NVX-CoV2373, as well as placebo and comparator arms.

In Study **2019nCoV-101 (Part 1)**, 131 subjects have been randomised and received either NVX-CoV2373 or placebo. No subject has experienced Treatment Emergent SAE.

In study **2019nCoV-101 (Part 2)**, 1,283 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced a total of 48 SAEs. The most frequent SAEs (5 or more PTs) experienced by subjects fall under the SOCs of Injury, Poisoning and Procedural Complications (8 PTs), Cardiac Disorders (7 PTs), Infections and Infestations (7 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (7 PTs), and Gastrointestinal Disorders (7 PTs).

In study **2019nCoV-301**, 29,582 adult subjects and 2,232 adolescents who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced a total of 1,916 SAEs. The most frequent SAEs (50 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (434 PTs), Cardiac Disorders (222 PTs),Respiratory, Thoracic and Mediastinal Disorders (151 PTs), Psychiatric Disorders (132 PTs), Injury, Poisoning and Procedural Complications (156 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (127 PTs), Nervous System Disorders (132 PTs), and Gastrointestinal Disorders (104 PTs), Hepatobiliary Disorders (63 PTs), Musculoskeletal and Connective Tissue Disorders (58 PTs), Renal and Urinary Disorders (59 PTs), General Disorders and Administration Site Conditions (57 PTs),Vascular Disorders (58 PTs) and Metabolism and Nutrition Disorders (51 PTs).

In study **2019nCoV-302**, 15,138 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 468 SAEs. The most frequently reported SAEs (25 or more PTs) experienced by subjects fall under the SOCs of: Infections and Infestations (96 PTs); Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) (77 PTs); Cardiac Disorders (53 PTs); Injury, Poisoning and Procedural Complications (46 PTs); Nervous System Disorders (37 PTs); and Gastrointestinal Disorders (26 PTs).

In study **2019nCoV-307**, 905 subjects who received NVX-CoV2373 with Matrix-M adjuvant experienced two SAEs that fell under the SOCs of Infections and Infestations (1 PT) and General disorders and administration site conditions (1 PT).

In study **2019nCoV-311**, 951 subjects who received NVX-CoV2373 with Matrix-M adjuvant or NVX-CoV2515 or bivalent vaccine experienced eight SAEs with most frequent AEs falling under the SOC of Infections and Infestations (2 PTs).

In study **2019nCoV-501**, 4,408 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 100 SAEs. . The most frequent SAEs (10 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (24 PTs) and Injury, Poisoning and Procedural Complications (15 PTs), and Pregnancy, Puerperium and Perinatal Conditions (10 PTs).

In study **2019nCoV-503**, 280 subjects received NVX-CoV2373 with Matrix-M adjuvant or placebo. No subjects experienced Treatment Emergent Adverse Event (TEAE) as of the DLP of this PBRER.

In study **2019nCoV-505**, 383 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 11 SAEs with most frequent SAEs falling under the SOCs of Psychiatric Disorders (3 PTs), pregnancy, puerperium and perinatal conditions (2 PTs) and Nervous System Disorders (2 PTs).

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

The term "medically confirmed" throughout this document is used to denote cases reported by an identified healthcare professional (HCP) of any type according to EMA GVP Module VI. It does not indicate that a reported event met a case definition, or that a medical condition has been confirmed by a physician with supporting diagnostic evidence.

Appendix 5 presents interval and cumulative count of serious and non-serious ICSRs for all spontaneous, regulatory authority, literature, and only serious ICSRs of NIS. 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.

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

During the 6-month reporting interval, 1,363 spontaneous ICSRs were received (of which 69 ICSRs were follow-ups), with 4,950 AEs (755 serious unlisted AEs, 259 serious listed AEs,

2,222 non-serious unlisted AEs, and 1,714 non-serious listed AEs). A total of 9 (8 initial and 1 follow-up) fatal ICSRs were reported during the reporting interval.

Of the 310 medically confirmed ICSRs received during the reporting interval, there were 119 serious ICSRs with 190 unlisted AEs (including 18 AEs with fatal outcome) and 72 listed AEs, and 191 non-serious ICSRs containing 338 unlisted and 271 listed AEs.

Of the 1,053 non-medically confirmed ICSRs (reporter is not identified as an HCP) received during the reporting interval, there were 246 serious ICSRs, containing 565 unlisted AEs, and 187 listed AEs, and 807 non-serious ICSRs containing 1,884 unlisted AEs, and 1,443 listed AEs.

Cumulatively, 3,161 spontaneous ICSRs containing 12,430 AEs have been received (of which 663 ICSRs were follow-ups). Of the 3,161 ICSRs received cumulatively, there were 652 serious ICSRs and 2,509 non-serious ICSRs. Of the 12,430 AEs received cumulatively, there were 1,927 serious AEs comprising 1,402 serious unlisted AEs (including fatal AEs), and 525 serious listed AEs, and 10,503 non-serious AEs comprising 5,845 non-serious unlisted AEs and 4,658 non-serious listed AEs. Cumulatively, 9 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 (BLA) by SK Bioscience Co., Ltd. The Korean Disease Control and Prevention Agency (KDCA) publishes the COVID-19 Vaccine Weekly Safety Report, which includes aggregate safety data for NUVAXOVID. Since individual case-level information is not available for downloading into the NVX safety database, the aggregate data is reviewed separately and is not included in pre-programmed O/E calculations.

This PBRER summarises cumulative data from the COVID-19 Vaccine Weekly Safety Report (Week 92) received during the reporting interval. A total of 908,103 NUVAXOVID doses were administered cumulatively as of 04-Dec-2022, with a corresponding total of 1,215 AEs as summarised in Table 11.

6.3.1.1 Adverse Events Following Immunisation by Nuvaxovid Listed by Symptoms

Table 11: Reports of Adverse Events following Administration of Nuvaxovid in South Korea

Symptoms Suspected to be Adverse Events (including duplicates)	Number of Cases
Myalgia	259
Headache	243
Dizziness	171
Chest pain	165
Allergic reaction	160
Vaccination Site Pain, Rash, Swelling within 3 days of vaccination	127
Queasy	110
Dyspnoea (Breathlessness)	92

Table 11: Reports of Adverse Events following Administration of Nuvaxovid in South Korea

Symptoms Suspected to be Adverse Events (including duplicates)	Number of Cases
Itching	86
Chills	79
Pyrexia	73
Vomiting	51
Cellulitis (Inflammation at the injection site, not an abscess)	36
Abdominal pain	35
Diarrhoea	30
Lymph gland infection	28
Arthritis	25
Abnormal uterine bleeding	25
Severe local adverse reactions	15
Acute paralysis	13
Anaphylactoid reaction	8
Acute Cardiovascular injuries	7
Vaccine associated enhanced disease	6
Anaphylactic reaction	4
Vaccination site abscess	4
Visual acuity reduced	3
Alopecia	3
Encephalopathy or Encephalitis	3
Thrombosis	3
Guillain-Barre syndrome	3
Acute aseptic arthritis	1
Acute liver injury	1
Anosmia	1
Convulsion (Convulsion/Seizure)	1
Acute renal injury	1
Multiple Organ inflammatory syndrome	1

Unit: cases

Three cumulative cases of myocarditis were referenced by KDCA in the COVID-19 Vaccine Weekly Safety Report (Week 92). The incidence rate of myocarditis in South Korea is currently reported as 0.3 cases per 100,000 vaccinations.

A review of suspected anaphylaxis cases (including anaphylactoid reaction cases) from 26-Feb-2021 to 22-Nov-2022 was conducted. A total of six cases were confirmed to have causal relationship with administration of Nuvaxovid, of which five were reported in female vaccinees

and one in a male vaccinee. The age range of five of the vaccinees (males and females) was between 30 – 59 years, while the other vaccinee (female) was either 19 years or younger.

Six cases (including duplicates) of vaccine associated enhanced disease (VAED) were reported. NVX does not have access to ICSRs from the KDCA for complete evaluation; however, due to an absence of any such cases in the global post-marketing setting outside of the KDCA report and no queries received from the KDCA regarding world-wide data on this topic, there is insufficient evidence as this time to suggest VAED represents a safety signal.

6.3.1.2 General Characteristics of Adverse Events which Resulted in Death

A total of 16 events in 7 individuals were reported as fatal, from a total of 908,103 doses administered. Characteristics of the fatal cases include vaccinees in the age range of 60 – 79 years (n=3) and 80 years and older (n=4) death occurring 2 days following vaccination for one vaccinee and 3 or more days following vaccination for the other 6 vaccinees. Details are provided in Table 12.

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

Table 12: Case Characteristics for Fatal Outcomes from South Korea

	Novavax	**Other COVID-19 Vaccine***
Total	7	28
Sex		
Male	3	22
Female	4	6
Age in years		
30 – 39	0	4
40 – 49	0	2
60 – 69	1	11
70 – 79	2	6
≥ 80	4	5
Underlying Medical Condition		
Yes	7	21
No	0	7
Time from Vaccination to Death		
< 1 day	0	3
1 day	0	1
2 days	1	1
≥ 3 days	6	23
Autopsy		
Done	0	6

Table 12: Case Characteristics for Fatal Outcomes from South Korea

	Novavax	**Other COVID-19 Vaccine***
Total	7	28
Sex		
Not Done	7	22

*Other: These are cross-vaccination cases from exposure to other COVID-19 vaccine types approved in South Korea (including Janssen x Pfizer, AstraZeneca x Moderna x Pfizer, Pfizer x Moderna, Janssen x Moderna, Sinopharm x Moderna, AstraZeneca x Moderna x Novavax, and Pfizer x Novavax).

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

7.1 Completed Clinical Trials

During the reporting interval, no clinical studies completed for NVX-CoV2373.

7.2 Ongoing Clinical Trials

During the reporting interval, 9 NVX-sponsored CTs are ongoing (seven studies in adults, one study in adolescents and one study in paediatric patient population). An overview of studies is summarised in Appendix 7 and Table 32. There were no emerging safety findings reported from the ongoing CTs. Safety, immunogenicity, and efficacy analysis results for ongoing CTs are summarised below.

7.2.1 Study 2019nCoV-101, Part 2

Study **2019nCoV-101, Part 2** was designed as a randomised, placebo-controlled, observer blinded study to reduce investigator and sponsor bias in the study. The primary objectives of Part 2 of this study are to identify the optimal dose based on immune response (IgG antibody to SARSCoV-2 rS) in a wider age range of healthy, adult subjects, building upon data collected in the Part 1, Phase 1 portion of the study. The current report summarises immunogenicity and safety data through 28 days following the 12-month booster vaccination (Day 371, data extracted 12-July-2022). Vaccine efficacy assessments for primary vaccination were not performed as the overall incidence of PCR-confirmed COVID-19 did not reach the predetermined threshold of 15% overall across all treatment groups during the study follow-up period (actual incidence: 8.8%).

Immunogenicity:

Two-dose regimens of 5 and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant, administered 21 days apart, induced robust immune responses 2 weeks after second vaccination (Day 35) versus one-dose regimens of either 5 µg or 25 µg adjuvanted vaccine, and placebo in healthy adult subjects ≥ 18 years.

- Anti-S protein IgG GMTs for the two-dose regimens (Group B [5/50 µg × 2], Group D [25/50 µg × 2], and the combination of Group B + D) were 44,393.8, 46,167.2, and 45,260.6 EU/mL, respectively, with GMFRs of 368.5, 365.1, and 366.8 relative to Group A (placebo Day 0/placebo Day 21) and 385.4, 381.9 and 383.6 relative to baseline (Day 0).

Booster administration of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant at 6 months and 12 months following a two-dose priming vaccination series on Days 0 and 21 (Group B2) induced robust immune responses in healthy adult subjects 18 to 84 years of age, with some attenuation of immune response in older subjects but with similar Seroconversion rates (SCRs) in both age cohorts.

- Serum IgG antibody GMTs at Day 217 in Group B2 (200,242.5 EU) were 31.2-fold greater than Day 189 titers and ~4.6-fold greater than titers reported following the primary vaccination series at Day 35.
    - At Day 217, an approximately ~1.9-fold increase in titers was observed in the younger vs older subject cohorts (266,769.1 EU vs 139,581.4 EU).
- Serum IgG antibody GMTs at Day 371 in Group B2 (214,152.3 EU) were 2.1-fold greater than Day 357 titers and ~1.07-fold greater than titers reported following the 6-month booster (Day 217).
    - At Day 371, older subjects had approximately ~1.49-fold higher titers vs the younger subject cohort (285,381.1 EU vs 190,915.8 EU), though this finding seemed to be due to the small sample size.
- Serum hACE2 receptor binding GMTs at Day 217 in in Group B2 (562.20 EU) were ~51.4-fold greater than Day 189 titers and ~7.2-fold greater than titers reported following the primary vaccination series at Day 35.
    - At Day 217, a ~2.1-fold increase in titers was observed in the younger vs older subject cohorts (775.29 vs 375.23 EU).
- Serum hACE2 receptor binding GMTs at Day 371 in Group B2 (544.54) were ~1.8-fold greater than Day 357 titers and roughly equivalent to titers reported following the 6-month booster (Day 217, 562.20 EU).
    - At Day 371, a somewhat narrower ~1.36-fold increase in titers was observed in the younger vs older subject cohorts (594.80 vs 436.70 EU)
- Neutralising antibody activity GMTs at Day 217 in Group B2 (5,542.1) were 81.1-fold greater than Day 189 titers and ~6.5-fold greater than titers reported following the primary vaccination series at Day 35.
    - At Day 217, an approximately ~1.8-fold increase in titers was observed in the younger vs older subject cohorts (7,167.7 vs 4,003.6).
- Neutralising antibody activity GMTs at Day 371 in Group B2 (6,891.0) were 1.9-fold greater than Day 357 titers and ~1.2-fold greater than titers reported following the 6-month booster (Day 217).
    - At Day 371, older subjects showed approximately ~1.1-fold higher titers vs the younger subject cohort (7,240.8 vs 6,755.9), though this finding seemed to be due to the small sample size.

Booster administration of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant at 12 months following a two-dose priming vaccination series on Days 0 and 21 (Group B1) induced robust immune responses in healthy adult subjects 18 to 84 years of age, with similar immune response in both young and older subject cohorts.

- Serum IgG antibody GMTs at Day 371 in Group B1 were higher when compared with those of their 4-dose, Group B2 counterparts (375,204.2 vs 214,152.3 EU).

  - At Day 371, older subjects showed approximately ~1.14-fold higher titers vs the younger subject cohort (402,202.7 vs 350,018.0 EU).

- Serum hACE2 receptor binding GMTs at Day 371 in Group B1 were higher when compared with those of their 4-dose, Group B2 counterparts (1,522.88 vs 544.54 EU).
  - At Day 371, older subjects showed approximately ~1.3-fold higher titers vs the younger subject cohort (1,728.03 vs 1,342.08 EU).

- Neutralising antibody activity GMTs at Day 371 in Group B1 were higher when compared with those of their 4-dose, Group B2 counterparts (17,221.6 vs 6,891.0).
  - At Day 371, younger subjects showed approximately ~1.4-fold higher titers vs the older subject cohort, and titers were overall quite elevated (20,480.0 vs 14,481.5). The unusually high titers seemed to be due to the small sample size.

Administration of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant 6 months following a single priming dose on Day 0 (Group C2) also induced robust immune responses in healthy adult subjects 18 to 84 years of age; however, immune responses following a single priming dose from Day 0 to Day 189 were much lower than those in subjects who received a two-dose priming series of active vaccine on Days 0 and 21. The results also indicated the gap between younger and older cohort subjects is somewhat reduced with an extended interval (6 month) dosing regimen.

- Serum IgG antibody GMTs at Day 217 in Group C2 (125,279.7 EU) were 378.1-fold greater than Day 189 titers and ~143.2-fold greater than titers reported following first vaccination (Day 35), indicating a strong memory induced response over the extended dosing interval (6 months).
  - At Day 217, an approximately ~1.3-fold increase in titers was observed for the younger vs older subject cohorts (141,922.3 EU vs 106,084.9 EU).

- Serum hACE2 receptor binding GMTs at Day 217 in Group C2 (406.84 EU) were ~75.5-fold greater than Day 189 titers and ~71.1-fold greater than titers reported following first vaccination (Day 35).
  - At Day 217, an approximately ~1.3-fold increase in titers was observed for the younger vs older subject cohorts (460.81 EU vs 344.59 EU).

- Neutralising antibody activity GMTs at Day 217 in Group C2 (3,403.1) were ~276.7-fold greater than Day 189 titers and ~153.3-fold greater than titers reported following first vaccination (Day 35).
  - At Day 217, an approximately ~1.2-fold increase in titers was observed for the younger vs older subject cohorts (3,620.4 vs 3,133.6.

Administration of 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant 12 months following a single priming dose on Day 0 (Group C1) induced robust immune responses in healthy adult subjects 18 to 84 years of age. Through 2 doses, the 12-month dosing interval produced higher titer overall but had a reduced effect in the older subject cohort.

- Serum IgG antibody GMTs at Day 371 in Group C1 (137,062.3 EU) were 536.6-fold greater than Day 357 titers and ~156.7-fold greater than titers reported following first vaccination (Day 35).
    - At Day 371, using data from the Sensitivity Analysis Set, an approximately ~12.5-fold increase in titers was observed for the younger vs older subject cohort (181,847.1 EU vs 14,511.9 EU), demonstrating a 12-month dosing interval results in markedly reduced immunogenicity for older subjects.
- Serum hACE2 receptor binding GMTs at Day 371 in Group C1 (368.35 EU) were ~53fold greater than Day 357 titers and ~64.4-fold greater than titers reported following first vaccination (Day 35), indicating a strong memory induced response over the extended dosing interval (12 months).
    - At Day 371, using data from the Sensitivity Analysis Set, an approximately ~6.9-fold increase in titers was observed for the younger vs older subject cohort (497.63 EU vs 72.50 EU).
- Neutralising antibody activity GMTs at Day 371 in Group C1 (4,305.4) were ~175.0-fold greater than Day 357 titers and ~193.9-fold greater than titers reported following first vaccination (Day 35).
    - At Day 371, using data from the Sensitivity Analysis Set, an approximately ~6.5-fold increase in titers was observed for the younger vs older subject cohort (6,558.1 vs 1,015.9).

Exploratory analysis to determine the effect of multiple booster doses of NVX-CoV2373 on immune responses generated against the ancestral, B.1.351 (Beta), B.1.617.2 (Delta), and BA.1 (Omicron) variant strains of SARS-CoV-2 in Group B2 subjects demonstrated a tendency for titers to converge with each subsequent boost.

- Serum IgG antibody levels:
    - Following their primary vaccination series at Day 35, Serum IgG antibody levels across the ancestral strain and the Beta, Delta, and Omicron variants were 43,904.7, 32,360.3, 22,388.9, and 9,298.5 EU, respectively. These figures corresponded with ancestral: variant ratios for the Beta, Delta, and Omicron variants of 1.36, 1.96, and 4.72, respectively.
    - After the 6-month booster vaccination at Day 217, titers for all viral strains were greatly elevated (200,242.5 [Ancestral], 171,116.7 [Beta], 160,607.6 [Delta], and 91,065.9 EU [Omicron]) and showed a tendency to converge (respective ancestral: variant ratios of 1.17, 1.25, and 2.20).
    - Following the 12-month booster at Day 371, serum IgG antibody levels increased again compared to Day 217 values (214,152.3 [Ancestral], 247,537.6 [Beta], 186,840.9 [Delta], 111,124.3 [Omicron]) with respective ancestral: variant ratios of 0.87, 1.15, and 1.93).

  - Across all variants, serum IgG antibody levels post-boost at Day 217 and Day 371 were at least ~2.07-fold greater than those reported at Day 35 for the ancestral strain (titers associated with high levels of efficacy in Phase 3 studies of the vaccine).

- Neutralising Antibody Activity:
  - Following their primary vaccination series at Day 35, titers across the ancestral strain and the Beta, Delta, and Omicron variants were 855.2, 37.5, 73.4, and 11.1, respectively. These figures corresponded with ancestral: variant ratios for the Beta, Delta, and Omicron variants of 22.8, 11.65, and 77.05, respectively.
  - After the 6-month booster vaccination at Day 217, titers for all viral strains were elevated (5,542.1 [Ancestral], 713.6 [Beta], 1,029.4 [Delta], and 82.3 [Omicron]) and showed a tendency to converge (respective ancestral: variant ratios of 7.77, 5.38, and 67.34).
  - Following the 12-month booster at Day 371, MN50 titers generally increased compared to Day 217 values (6,891.0, [Ancestral], 1,560.3 [Beta], 861.4 [Delta], 142.5 [Omicron]), and ancestral: variant ratios converged again, but remained distant (respective ancestral: variant ratios of 4.42, 8.00, and 48.36).
  - Serum MN50 titers post-boost at Day 217 and Day 371 approached or exceeded the Day 35 titers seen for the ancestral strain for all SARS-CoV-2 variants except Omicron.
- Subjects in Group B1 at Day 189 who received 3 doses NVX-CoV2373 throughout the study (a 2-dose primary series (Day 0 and Day 21), and a single boost at Day 357) demonstrated higher Day 371 titers across all variants when compared to their 4-dose, Group B2 counterparts. Serum IgG antibody levels were consistently ~1.75-fold greater, while the gap for MN_{50} titers varied across strains (2.5 [Ancestral], 1.16 [Beta], 2.97 [Delta], and 2.24 [Omicron]).

Post-hoc analysis to test for non-inferiority of serum IgG antibody levels and MN50 titers post-boost at Day 217 and Day 371 versus Day 35 met each success criterion (lower limit of 95% CI > 0.67 for GMT ratio comparison and lower limit of 95% CI > -10% for SCR comparison).

- Day 217 vs Day 35 GMT ratios were 4.7 (95% CI: 3.8, 5.9) and 4.0 (95% CI: 2.5, 6.5) for IgG and MN_{50} titers, respectively.
  - Day 217 vs Day 35 SCRs versus Day 0 were each 100%, for a difference of 0.0%.
- Day 371 vs Day 35 GMT ratios were 5.3 (95% CI: 2.3, 12.2; for the PP Analysis Set) and 3.7 (95% CI: 1.6, 8.5; for the Sensitivity Analysis Set) for IgG and MN_{50} titers, respectively.
  - Day 371 vs Day 35 SCRs versus Day 0 were 100% for MN50 titers, but for serum IgG titers there was a difference of -2.9%, which met the success criterion (lower limit of 95% CI > -10%). It was discovered that this difference in SCR was due to an anomalous sample error whereby subject [redacted] had Day 371 IgG titers reported as below the LLOQ. Upon retest, the subject's Day 371 IgG titer was 68,030 EU/mL

Safety:

The key safety conclusions at the time of the Day 385 Interim Analysis were:

- Up to 4 doses of 5 µg SARS-CoV-2 rS with 50-µg Matrix-M adjuvant administered at Day 0, Day 21, Day 189, and Day 357 were well tolerated in healthy adult subjects 18 to 84 years of age.
- Subjects receiving multiple active vaccinations (Group B1, Group B2, Group C1, Group C2, and Group D) reported solicited local and systemic AEs at higher frequencies and with higher intensity with subsequent vaccinations through Dose 1, Dose 2, and Dose 3. Dose 4 (12-month booster in Group B2) showed similar reactogenicity to Dose 3.
    - Solicited local reactions following Dose 1, Dose 2, Dose 3, and Dose 4 in Group B2 were reported by 51.8% (0.4% ≥ Grade 3), (70.0% (5.2% ≥ Grade 3), 82.5% (13.4% ≥ Grade 3), and 73.2% (19.5% ≥ Grade 3) of subjects, respectively.
    - Solicited systemic reactions following Dose 1, Dose 2, Dose 3, and Dose 4 in Group B2 were reported by 43.9% (3.9% ≥ Grade 3), (52.8% (5.6% ≥ Grade 3), 76.5% (15.3% ≥ Grade 3), and 68.3% (17.1% ≥ Grade 3) of subjects, respectively.
- Median durations of the most common solicited local and systemic events were ≤ 3.0 days without appreciable change in duration following booster vaccinations.
- Subjects receiving active vaccine at Dose 3 and Dose 4 had a lower incidence of TEAEs occurring through 28 days after boost vaccination vs the 35 days following primary vaccination, which seemed to be in line with the shorter timeframe for collection.
    - Frequencies of unsolicited TEAEs reported through 35 days after first vaccination (18.8%, 22.9%, 15.6%, 21.6%, and 20.4%, respectively, for Groups A, B, C, D, and E) were higher overall than during the 28 days following the 6-month booster vaccination (11.0%, 12.7%, 12.4%, 7.0%, 9.6%, 6.1%, and 9.7%, respectively, for Groups A, B1, B2, C1, C2, D, and E) and the 12-month booster vaccination (6.1%, 8.9%, 3.7%, and 8.8%, respectively, for Groups B1, B2, C1, and C2).
- Frequencies of severe unsolicited TEAEs were uncommon across the study, with frequencies of 1.2%, 1.2%, 1.6%, 0%, and 0%, respectively, in Groups A, B, C, D, and E through 35 days after first vaccination and frequencies of 0%, 1.0%, 0%, 0%, 1.0%, 0%, and 0%, respectively, in Groups A, B1, B2, C1, C2, D, and E from 6-month booster vaccination through 28 days after booster vaccination. No severe unsolicited TEAEs were reported following the 12-month booster vaccination.
- Treatment-related, unsolicited TEAEs were rare across the study, reported by 58 (4.5%) subjects [7.3%]) compared to the other treatment groups (9 [3.5] % in Group A, 8 [5.2%] in Group B1, 5 [3.3%] in Group C1, 2 [1.9%] in Group C2, and 6 [2.4%] in Group E).
    - There were higher frequencies of unsolicited treatment-related TEAEs during the 28 days following the 12-month booster vaccination (6.1%, 8.9%, 3.7%, and 0%, respectively, for Groups B1, B2, C1, and C2) than through 35 days after first vaccination (3.1%, 2.3%, 1.2%, 5.8%, and 1.6%, respectively, in Groups A, B, C, D, and E) or during the 28 days

following the 6-month booster vaccination (0.6%, 1.0%, 3.8%, 0%, 1.9%, 0.5%, and 1.0%, respectively, for Groups A, B1, B2, C1, C2, D, and E)

- No subject had a severe, treatment-related, unsolicited TEAE throughout the study.

- SAEs were reported in 39 (3.0%) subjects overall with Group A (5 [2.0%]), Group B1 (6 [3.9%]), Group B2 (7 [6.7%]), Group C1 (6 [3.9%]), Group C2 (3 [2.9]), Group D (5 [1.9%]), and Group E (7 [2.7%]) subjects reporting events with similar, low frequencies.
  - Two (0.2%) subjects had SAEs that were assessed by the investigator as related to trial vaccine (1 in Group C1 [colitis] and 1 in Group D [microscopic colitis]).

7.2.2 Study 2019nCoV-301

Study **2019nCoV-301** is an ongoing Phase 3, randomised, observer-blind, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of SARS-CoV-2 recombinant spike protein nanoparticle vaccine with Matrix M adjuvant in adult subjects ≥ 18 years of age in USA and Mexico. The most recent interim report includes all efficacy and safety data accumulated in the Adult Main Study from the initiation of the study to the data cut-off on 27-Sep-2021, except for immunogenicity data which will be reported separately.

Efficacy:

- A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart in the Initial Vaccination Period, met the prespecified study success criterion of the final primary efficacy outcome measure versus placebo in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects.
- Statistically significant VE = 90.41% (95% CI: 83.81, 94.32) for the final analysis of the primary endpoint; p-value < 0.0001
- Statistically significant VE = 96.57% (95% CI: 73.78, 99.55) for the key secondary endpoint for efficacy against mild, moderate, or severe PCR-confirmed COVID-19 due to non-VOC/VOI; p-value = 0.0018
- There were no moderate or severe cases of COVID-19 among NVX-CoV2373 recipients resulting in a statistically significant VE of 100.00% (95% CI: 85.41, 100.00); p-value < 0.0001
- High VEs for the following subgroups of the primary endpoint: − Subjects 18 to < 65 years of age: 91.06% (95% CI: 84.44, 94.87) − High-risk subjects: 90.87% (95% CI: 84.38, 94.67)
- Subgroup analysis of additional demographic and baseline conditions yielded VEs consistent with that reported for the primary efficacy endpoint; however, there were too few cases of COVID-19 for the remaining demographic characteristics and COVID-19 risk conditions (including subjects ≥ 65 years of age and non-high-risk subjects) to allow meaningful interpretation of vaccine efficacy.
- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to a SARS-CoV-2 variant considered or not considered a Variant of Concern (VOC)

or Variant Being Monitored (VBM) with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects.

- VE = 96.57% (95% CI: 73.78, 99.55) due to a SARS-CoV-2 variant not considered as a VOC or VBM.
- VE = 93.26% (95% CI: 85.84, 96.80) due to a SARS-CoV-2 variant considered as a VOC or VBM.
- NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects.
- VE = 100.00% (95% CI: 85.41, 100.00), p-value < 0.0001. Cumulative rates of PCR-confirmed symptomatic mild, moderate, and severe COVID-19 begin to diverge at approximately 21 days after first vaccination. Cumulative rates of PCR-confirmed symptomatic moderate and severe COVID-19 began to diverge at approximately 3 months after first vaccination.

Safety:

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered at least 21 days apart, was well tolerated and had an acceptable safety profile in adult subjects ≥ 18 years of age in both the initial and blinded crossover vaccination periods.

- Approximately 96% of NVX-CoV2373 recipients received both doses of trial vaccine in the initial vaccination period, with 97.3% of subjects 18 to < 65 years of age and 93.3% of subjects ≥ 65 years of age receiving both doses of NVX-CoV2373. Of the subjects who crossed over to receive the opposite treatment during the blinded crossover vaccination period, 99% received both doses of trial vaccine with 98.8% of subjects 18 to < 65 years of age and 99.7% of subjects ≥ 65 years of age crossing over from placebo in the initial vaccination period to receive both doses of NVX-CoV2373 during the blinded crossover vaccination period.
- Median follow-up was 2.5 months after second vaccination in the initial vaccination period and 4.4 months after second vaccination in the blinded crossover vaccination period.
- NVX-CoV2373 recipients reported higher frequencies and intensities of solicited injection site and systemic adverse reactions than placebo recipients, especially after the second vaccination of the initial vaccination period (solicited adverse reactions were not recorded during the blinded crossover vaccination period). This trend was observed in both age cohorts, 18 to < 65 years of age and ≥ 65 years of age, with lower frequencies and intensities of solicited injection site and systemic adverse reactions in the older age cohort.
- The median onset of solicited local injection site adverse reactions reported in both NVX-CoV2373 and placebo recipients was Day 2 (Day 1 of the trial), with a median duration of 2 days in the NVX-CoV2373 group and 1 day in the placebo group. Solicited local injection site adverse reactions that persisted beyond the 7-day reactogenicity period were reported more frequently in the NVX-CoV2373 group than in the placebo group.

- The median onset of solicited systemic adverse reactions in both NVX-CoV2373 and placebo recipients overall was Day 2 (Day 1 of the trial), with a median onset of joint pain of Day 3 (Day 2 of the trial) and fever of Day 4 (Day 3 of the trial). Solicited systemic adverse reactions that persisted beyond the 7-day reactogenicity period were reported more frequently in the NVX-CoV2373 group than in the placebo group.
- Most NVX-CoV2373 recipients (> 85%) who reported injection site and systemic adverse reactions experienced Grade 1 or Grade 2 reactions, with Grade 3 or Grade 4 local injection site adverse reactions reported in less than 10% of subjects and Grade 3 or Grade 4 systemic adverse reactions reported in less than 15% of subjects.
- Tenderness and pain were the most frequently reported solicited injection site reactions and fatigue, headache, muscle pain, and malaise were the most frequently reported systemic adverse reactions.
- Unsolicited AEs were reported in less than 15% of NVX-CoV2373 recipients during the initial vaccination period and in less than 10% of NVX-CoV2373 recipients during the blinded crossover vaccination period. Most unsolicited AEs were mild or moderate in severity, with few subjects (< 1%) reporting severe AEs.
- There were similar frequencies and intensities of unsolicited AEs among both NVX-CoV2373 and placebo recipients during the initial vaccination period, with the exception of unsolicited AEs of the SOC General Disorders and Administration Site Conditions which had a higher frequency among NVX-CoV2373 recipients than placebo recipients, largely attributable to reactogenicity reactions. For the blinded crossover vaccination period, frequencies of unsolicited AEs were generally higher among NVX-CoV2373 recipients than placebo recipients for SOCs comprising AEs consistent with reactogenicity reactions.
- Related unsolicited AEs were reported at a higher frequency among NVX-CoV2373 recipients than placebo recipients in both the initial and blinded crossover vaccination periods, generally attributable to reactogenicity-like reactions.
- There were similar frequencies of MAAEs, SAEs, AESIs, deaths, and AEs leading to vaccine discontinuation reported in both NVX-CoV2373 and placebo recipients in both the initial and blinded crossover vaccination periods, with few subjects reporting treatment-related SAEs, AESIs (PIMMCs or those related to COVID-19), deaths, or AEs leading to vaccine discontinuation.

7.2.3 Study 2019nCoV-301 Adult Booster

Study **2019nCoV-301** Adult Booster assessed the immune response (neutralising antibody against SARS-CoV-2 wild-type virus, serum immunoglobulin G (IgG) antibody to SARS-CoV-2 S protein, and human angiotensin-converting enzyme 2 (hACE2) receptor binding inhibition to SARS-CoV-2 rS) immediately prior to and at 28 days after administration of a third (booster) dose of NVX-CoV2373 and the overall safety of NVX-CoV2373 through 28 days after the booster dose. This ad-hoc analysis was conducted for a randomly selected 298 adult subjects (142 who received a booster dose after active vaccination during the blinded crossover period [Cohort 1] and 156 who received a booster dose after active vaccination during the initial vaccination period [Cohort 2]) from 7 sites in the US where a blood sample for immunogenicity

was collected at 14 days post the second crossover vaccination dose. Booster efficacy was not included in this analysis.

Immunogenicity:

A single booster dose of NVX-CoV2373, administered at 8.1 months (Cohort 1) and 11.2 months (Cohort 2) after the second dose (primary series) of NVX-CoV2373, elicited robust immune responses (neutralising antibody, serum IgG antibody, and hACE2 receptor binding inhibition) against the ancestral Wuhan strain at 28 days after booster vaccination that were higher than those reported at 14 days after primary series vaccination in adult subjects. Non-inferiority was achieved for the ratio of neutralising antibody GMTs (GMFR) but not for the differences in SCRs, with the latter confounded by higher neutralising antibody GMTs prior to booster administration compared to the neutralising antibody GMTs prior to the first dose of active vaccine. Higher immune responses (neutralising antibody and serum IgG antibody) were also seen after the single booster dose against the Omicron BA.1 variant in a subset of subjects.

- Neutralising Antibody Titers Against the SARS-CoV-2 Wild-Type Virus
  - Neutralising antibody GMTs were higher at 28 days after booster administration (4,235.8 and 5,972.6 in Cohort 1 and Cohort 2, respectively) than at 14 days after the primary series (1,162.3 and 1,914.3, respectively) for all subjects and by age group.

    18 to < 65 years: 4,243.1 vs 1,246.6 (Cohort 1) and 6,119.0 vs 2,425.8 (Cohort 2)

    ≥ 65 years: 4,158.7 vs 557.2 (Cohort 1) and 5,291.8 vs 599.1 (Cohort 2)

    ≥ 50 years: 3,753.9 vs 959.8 (Cohort 1) and 5,696.2 vs 1,473.5 (Cohort 2)
  - Non-inferiority was achieved for the ratio of neutralising antibody GMTs (GMFR), with LBs of the 95% CI > 1.0 (2.9 and 2.5, respectively, in Cohort 1 and Cohort 2) in all subjects and by age group.
  - Neutralising antibody SCRs were lower at 28 days after booster administration (87.2% in Cohort 1 and 83.3% in Cohort 2) than at 14 days after the primary series (92.2% in Cohort 1 and 96.8% in Cohort 2) in all subjects and by age group.

    18 to < 65 years: 86.9% vs 94.3% (Cohort 1) and 83.8% vs 100.0% (Cohort 2)

    ≥ 65 years: 90.0% vs 70.0% (Cohort 1) and 81.0% vs 81.0% (Cohort 2)

    ≥ 50 years: 88.1% vs 87.7% (Cohort 1) and 86.2% vs 93.8% (Cohort 2)
  - Non-inferiority was not achieved for the difference in neutralising antibody SCRs, with LBs of the 95% CI not > -10% (-12.7% and -20.5%, respectively, in Cohort 1 and Cohort 2) for all subjects. This finding was confounded by higher neutralising antibody GMTs prior to booster administration (125.5 and 221.3, respectively, for Cohort 1 and Cohort 2) compared to the neutralizing antibody GMTs prior to the first dose of active vaccine (12.3 and 11.4, respectively).
  - There was less attenuation of neutralising antibody response in the younger age group (18 to 64 years) compared with the older age group (≥ 65 years) after booster

administration (1.0- and 1.2-fold, respectively, in Cohort 1 and Cohort 2) than after the primary series (2.2- and 4-fold, respectively), suggesting increased sensitization of immune response in older subjects after boosting.

- Neutralising antibody GMTs against the Omicron BA.1 variant were higher at 28 days after booster administration (235.2) than at 14 days after the primary series (13.6) in a subset of subjects.

- Serum IgG Antibody to SARS-CoV-2 S Protein
  - Serum IgG antibody GMEUs were higher at 28 days after booster administration (150,423.5 and 219,924.1 EU/mL in Cohort 1 and Cohort 2, respectively) than at 14 days after the primary series (41,126.5 and 68,692.8 EU/mL, respectively) for all subjects and by age group.

    18 to < 65 years: 152,959.7 vs 43,229.3 EU/mL (Cohort 1) and 246,343.3 vs 84,446.2 EU/mL (Cohort 2)

    ≥ 65 years: 125,782.5 vs 24,241.4 EU/mL (Cohort 1) and 127,976.6 vs 25,641.7 EU/mL (Cohort 2)

  - Serum IgG antibody SCRs were lower at 28 days after booster administration (87.2% in Cohort 1 and 82.7% in Cohort 2) than at 14 days after the primary series (95.7% in Cohort 1 and 98.4% in Cohort 2) in all subjects. This finding was confounded by higher serum IgG antibody GMEUs prior to booster administration (4,805.3 and 8,166.7 EU/mL, respectively, for Cohort 1 and Cohort 2) compared to the serum IgG antibody GMEUs prior to the first dose of active vaccine (142.4 and 125.5 EU/mL, respectively).
  - There was less attenuation of serum IgG antibody response in the younger age group (18 to 64 years) compared with the older age group (≥ 65 years) after booster administration (1.2- and 1.9-fold in Cohort 1 and Cohort 2, respectively) than after the primary series (1.8- and 3.3-fold in Cohort 1 and Cohort 2, respectively), suggesting increased sensitisation of immune response in older subjects after boosting.
  - Serum IgG antibody GMEUs against the Omicron BA.1 variant in Cohort 2 were higher at 28 days after booster administration (147,664.5 EU/mL) than at 14 days after the primary series (17,909.3 EU/mL) in a subset of subjects.

- hACE2 Receptor Binding Inhibition to SARS-CoV-2 rS
  - hACE2 receptor binding inhibition GMT in Cohort 2 was higher at 28 days after booster administration (553.7) than at 14 days after the primary series (245.9) for all subjects and by age group.

    18 to < 65 years: 585.8 vs 298.1 (Cohort 2)

    ≥ 65 years: 423.0 vs 98.1 (Cohort 2)

  - hACE2 receptor binding inhibition SCRs in Cohort 2 were lower at 28 days after booster administration (81.1%) than at 14 days after the primary series (94.5%) in all subjects.

This finding was confounded by a higher hACE2 receptor binding inhibition GMT prior to booster administration (23.8) compared to the hACE2 receptor binding inhibition GMT prior to the first dose of active vaccine (5.3).

- There was less attenuation of hACE2 receptor binding inhibition in Cohort 2 in the younger age group (18 to 64 years) compared with the older age group (≥ 65 years) at 28 days after booster administration (1.4-fold) than after the primary series (3.0-fold), suggesting increased sensitisation of immune response in older subjects after boosting.

Safety:

A single booster dose of NVX-CoV2373, administered at 8.1 months (Cohort 1) and 11.2 months (Cohort 2) after the second dose (primary series) of NVX-CoV2373 appeared to be well tolerated with no safety concerns from the time of booster administration through 28 days after booster administration.

- Solicited local and systemic TEAEs were reported in most subjects in Cohort 1 and Cohort 2, with most subjects reporting Grade 1 or Grade 2 TEAEs.
  - Among individual solicited TEAEs, there was a trend toward higher frequencies of Grade ≥ 3 solicited local TEAEs in Cohort 2 than in Cohort 1 and a trend toward higher frequencies of any grade (Grade ≥ 1) and Grade ≥ 3 solicited systemic TEAEs in Cohort 2 than in Cohort 1; this finding may possibly be due to the higher immune responses observed after booster administration in Cohort 2 compared with Cohort 1.
  - For both cohorts, tenderness and pain were the most frequent (incidence > 10%) solicited local TEAEs and muscle pain, fatigue, headache, malaise, arthralgia, and nausea/vomiting were the most frequent solicited systemic TEAEs.
  - Fatigue and malaise were the most frequent Grade ≥ 3 solicited TEAEs. Grade 4 solicited TEAEs were reported for solicited systemic TEAEs in Cohort 2 only.
  - No subject in either cohort had a solicited local or systemic TEAE with an onset after 7 days from booster vaccination.
  - Similar patterns of response were seen within each age group, but there were higher frequencies of any grade (Grade ≥ 1) and Grade ≥ 3 solicited local and systemic TEAEs in the younger age group (18-64 years) than in the older age group (≥ 65 years).
  - Frequencies of solicited local and systemic TEAEs, any grade (Grade ≥ 1) and Grade ≥ 3, generally increased with each successive dose of NVX-CoV2373 with most TEAEs being Grade 1 or Grade 2 in severity, with more frequent events reported in the younger age group (18-64 years) than in the older age group (≥ 65 years).
- Unsolicited TEAEs through 28 days after the third (booster) dose of NVX-CoV2373 were reported in 7 (4.9%) subjects in Cohort 1 and in 4 (2.6%) subjects in Cohort 2, with no reports of severe TEAEs, TEAEs leading to study discontinuation or resulting in death, or AESIs (including PIMMCs and COVID-19 related TEAEs. SAEs were reported in no

subjects in Cohort 1 and 2 subjects in Cohort 2; the SAEs in Cohort 2 were assessed by both the investigator and sponsor as not related to study vaccine

- All unsolicited TEAEs were mild or moderate in severity.
- Related unsolicited TEAEs were reported in 3 (2.1%) subjects in Cohort 1 and included events of lymphadenopathy, injection site pain, and neuralgia; no subject in Cohort 2 reported a related unsolicited TEAE.
- MAAEs were reported in 3 (2.1%) subjects in Cohort 1 and in 4 (2.6%) subjects in Cohort 2. All MAAEs were unique in each cohort. The majority of MAAEs in the cohorts were moderate in severity, with no severe events, and were assessed by the investigator as not related.

7.2.4 Study 2019nCoV-301 Adolescent Booster

Study **2019nCoV-301** Adolescent Booster was initiated on 26-Apr-2021 (first subject randomised) to 05-Jun-2021 (last subject randomised) at 73 sites across the US, and the blinded crossover vaccination period commenced on 06-Aug-2021 and completed enrollment on 06-Dec-2021. The open-label single-dose booster vaccination period of the Pediatric Expansion was initiated on 04-Apr-2022 and completed enrollment on 12-May-2022. An ad-hoc analysis was conducted with a subset of 220 subjects from 60 sites in the US who completed the Day 28 booster visit. These subjects comprised a restricted data set with a data cut-off date of 16-Jun-2022; an unrestricted data set included all adolescent subjects (N =1499) who received a booster dose of NVX-CoV2373. (The term "restricted" refers to all the data cleaned through the data cutoff date, whereas "unrestricted" refers to all data through the date of data extraction [not necessarily all cleaned]) on 07-Sep-2022. For the ad-hoc analysis, immunogenicity and safety data were collected from the time of the booster vaccination through 28 days after booster vaccination based on a data extraction date of 07-Sep-2022. Booster efficacy was not included in this analysis. Only subjects in Cohort 2 were included in the immunogenicity analysis. The study remains ongoing, with follow up through 2 years post immunisation.

Immunogenicity:

A single booster dose of NVX-CoV2373 administered to adolescent subjects 12 to < 18 years elicited robust immune responses (neutralising antibody, serum IgG antibody, and hACE2 receptor binding inhibition) against the ancestral Wuhan strain at 28 days after booster vaccination that were higher than those reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series. Non-inferiority was achieved for GMFRs and for the differences in SCRs using the baseline of the first dose of NVX-CoV2373 in the pre-crossover period (Cohort 2), with the former due to higher neutralising antibody GMTs prior to booster administration compared to the neutralising antibody GMTs prior to the first dose of NVX-CoV2373. For Cohort 2, higher immune responses for serum IgG antibody against the Omicron BA.1 Variant were also seen after the third (booster) dose of NVX-CoV2373.

- Comparison of Cohort 2 Neutralising Antibody Titers Against the SARS-CoV-2 Wild-Type Virus (Ancestral Wuhan Strain) After Booster Administration (Compared with Primary Vaccination) in Adolescents
  - For Cohort 2 a robust neutralising antibody (MN50) response against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series (neutralising antibody GMTs of 11,824.4 and 4434.0, respectively).
  - For Cohort 2 non-inferiority was achieved for the comparison between the neutralising antibody (MN50) response against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series, with a GMFR of 2.7 (95% CI: 2.0, 3.5) and an LB of the 95% CI > 1.0.
  - For Cohort 2, SCRs for neutralising antibody titers against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and those reported at 14 days after the second dose of NVX-CoV2373 of the primary series, both relative to the first dose of NVXCoV2373, were 100.0% and 100.0%, respectively.
  - For Cohort 2, the difference in SCRs for neutralising antibody against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary series, both relative to the first dose of NVX-CoV2373, supported non-inferiority, with an LB of the 95% CI > -10% (the analysis showed a difference of 0.0% [95% CI: -6.8 to 6.8]).
- Increased Serum IgG Antibody to SARS-CoV-2 Spike Protein (Ancestral Wuhan Strain) after Booster Administration (Compared with Primary Vaccination) in Adolescents
  - For Cohort 2 a robust serum IgG antibody response against the SARS-CoV-2 spike protein (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series (GMEUs of 388,263.3 and 156,286.4 EU/mL, respectively).
  - For Cohort 2 the comparison between the IgG antibody response against the SARS-CoV-2 spike protein (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series yielded a GMFR of 2.5 (95% CI: 2.1 to 3.0).
  - For Cohort 2, SCRs for serum IgG antibody against the SARS-CoV-2 spike protein (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and

that reported at 14 days after the second dose of NVX-CoV2373 of the primary series, both relative to the first dose of NVX-CoV2373, were 100.0% and 100.0%, respectively.

- Increased hACE2 Receptor Binding Inhibition to SARS-CoV-2 rS (Ancestral Wuhan Strain) after Booster Administration (Compared with Primary Vaccination) in Adolescents
  - For Cohort 2 a robust hACE2 receptor binding inhibition to SARS-CoV-2 rS (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series (receptor binding inhibition GMTs of 1,050.8 and 519.7 titer units, respectively).
  - For Cohort 2 the comparison between the hACE2 receptor binding inhibition to SARS-CoV-2 rS (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series yielded a GMFR of 2.0 (95% CI: 1.7 to 2.5).
  - For Cohort 2, SCRs for hACE2 receptor binding inhibition to SARS-CoV-2 rS (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series, both relative to the first dose of NVX-CoV2373, were 100.0% and 100.0%, respectively.
  - For Cohort 2, the difference between SCRs for hACE2 receptor binding inhibition to SARS-CoV-2 rS (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series, both relative to the first dose of NVX-CoV2373, was 0.0% (95% CI: -6.2 to 6.2).
- Increased Serum IgG Antibody to SARS-CoV-2 Spike Protein (Omicron BA.1 Variant) after Booster Administration (Compared with Primary Vaccination) in Adolescents
  - For Cohort 2 a robust serum IgG antibody response against the SARS-CoV-2 spike protein (Omicron BA.1 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series (GMEUs of 330,102.7 and 41,178.0 EU/mL, respectively), yielding a GMFR of 8.0 (95% CI: 6.7 to 9.6).
  - For Cohort 2, SCRs for serum IgG antibody against the SARS-CoV-2 spike protein (Omicron BA.1 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary series, both relative to the first dose of NVX-CoV2373, were 100.0% and 100.0%, respectively.
  - For Cohort 2 the difference between SCRs for serum IgG antibody against the SARS-CoV-2 spike protein (Omicron BA.1 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series, both relative to the first dose of NVX-CoV2373, was 0.0% (95% CI: -6.2 to 6.2).

- Increased Pseudovirus-Based Neutralisation Antibody to SARS-CoV-2 Spike Protein (Omicron BA.14/5 Variant) after Booster Administration (Compared with Primary Vaccination) in Adolescents
    - For Cohort 2, a single booster dose of NVX-CoV2373 after the second dose (primary series) of NVX-CoV2373 in adolescent subjects elicited a robust pseudovirus-based neutralising antibody (ID50) response against the SARS-CoV-2 spike protein (Omicron BA.4/5 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 that was also higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series (neutralising antibody GMTs of 4,081.8 and 404.7, respectively) yielding a GMFR of 10.1 (95%CI: 6.7, 15.1).
    - For Cohort 2, the SCRs for pseudovirus-based neutralising antibody against SARS-CoV-2 spike protein (Omicron BA.4/5 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 relative to the first dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 relative to the first dose of NVX-CoV2373 in the primary vaccination series were 100.0% and 87.5%, respectively.
    - For Cohort 2, the difference in SCR for pseudovirus-based neutralising antibody against SARS-CoV-2 spike protein (Omicron BA.4/5 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 and that reported at 14 days after the second dose of NVX-CoV2373 in the primary vaccination series, both relative to the first dose of NVX-CoV2373 was 12.5% (95% CI: -3.0, 31.0).

Safety:

- A single booster dose of NVX-CoV2373, administered to adolescent subjects 12 to < 18 years after the second dose (primary series) of NVX-CoV2373 appeared to be well tolerated with no safety concerns from the time of booster administration through 28 days after booster administration.
- Solicited local and systemic TEAEs were reported in most subjects, with most subjects reporting Grade 1 or Grade 2 TEAEs.
- Solicited local and systemic TEAEs were reported in 80.5% and 85.8% of adolescent subjects, respectively, with the majority of subjects (59.5%) reporting events of Grade 1 or Grade 2 severity.
- Each solicited local and systemic TEAE was reported in at least 10% of subjects, with tenderness and pain (local) and headache, fatigue, muscle pain, malaise, and nausea/vomiting (systemic) being the most frequent (incidence > 25% subjects).
- Fatigue and malaise were the most frequent (incidence > 15% subjects) Grade ≥ 3 solicited TEAEs; no Grade 4 solicited TEAEs were reported.
- No adolescent subject had a solicited local or systemic TEAE with an onset after 7 days from booster vaccination.
- Frequencies of solicited local and systemic TEAEs, any grade (Grade ≥ 1) and Grade ≥ 3, generally increased with each successive dose of NVX-CoV2373. Tenderness and pain were the most frequent (incidence > 10% across the primary and booster vaccination periods)

solicited local TEAEs, and muscle pain, fatigue, headache, and malaise were the most frequent solicited systemic TEAEs.

- Unsolicited TEAEs among the 220 subjects of the restricted population through 28 days after the third (booster) dose of NVX-CoV2373 were reported in 11 (5.0%) adolescent subjects, with a severe TEAE reported in 1 (0.5%) subject, and no TEAE leading to study discontinuation, resulting in death, or AESI (including PIMMCs and COVID19 related TEAEs). One (0.5%) subject reported an SAE of cholelithiasis; the SAE was assessed by both the investigator and sponsor as not related to study vaccine.
- Two (0.9%) subjects each reported TEAEs of lymphadenopathy and oropharyngeal pain, with the remaining subjects reporting unique TEAEs.
- Eight (3.6%) adolescent subjects reported mild TEAEs, 2 (0.9%) adolescent subjects reported moderate TEAEs, and 1 (0.5%) adolescent subject reported a severe TEAE. The severe TEAE was cholelithiasis, which was also an SAE.
- Related unsolicited TEAEs through 28 days following the third (booster) dose of NVX-CoV2373 were reported in 4 (1.8%) adolescent subjects and included 2 (0.9%) subjects with a TEAE of lymphadenopathy and 1 (0.5%) subject each with a TEAE of body temperature increased and oropharyngeal pain.
- No adolescent subject died through 28 days following the third (booster) dose of NVXCoV2373.
- No adolescent subject had an AESI through 28 days following the third (booster) dose of NVX-CoV2373, including PIMMCs reported by the site and based on protocol-defined criteria and COVID-19 related TEAEs.
- MAAEs through 28 days following the third (booster) dose of NVX-CoV2373 were reported in 3 (1.4%) adolescent subjects and included unique TEAEs of cholelithiasis, upper respiratory tract infection, and hand fracture.
- The MAAEs were moderate in severity, except for 1 severe event of cholelithiasis, and were assessed by the investigator as not related to study vaccine.
- NOTE: Among the 1499 subjects of the unrestricted population through 28 days after the third (booster) dose of NVX-CoV2373, unsolicited TEAEs were reported in 77 (5.1%) adolescent subjects, with severe TEAEs reported in 5 (0.3%) subjects and no TEAE resulting in death.
- Three (0.2%) subjects reported SAEs, including those of cholelithiasis, type 2 diabetes mellitus, and suicide attempt; the SAEs were assessed by both the investigator and sponsor as not related to study vaccine.
- Three [0.2%] of 1499 subjects had a TEAE leading to study discontinuation.
- No adolescent subject had an AESI, including PIMMCs reported by the site and based on protocol-defined criteria of Protocol 2019nCoV-301.
- COVID-19 related TEAEs were reported in 7 (0.5%) subjects.
- MAAEs were reported in 34 (2.3%) adolescent subjects.

7.2.5 Study 2019nCoV-302

Study **2019nCoV-302** is a Phase 3, randomised, observer-blinded, placebo-controlled study evaluating the efficacy, safety, and immunogenicity of two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS co-formulated with 50 µg Matrix-M adjuvant), administered 21 days apart in adult subjects 18 to 84 years of age in the UK.

Efficacy:

A two-dose regimen of NVX-CoV2373, administered 21 (+ 7) days apart, prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) healthy and clinically stable adult subjects at baseline in the UK at a time when the B.1.1.7 (Alpha) variant of SARS-CoV-2 was predominant, with VEs of nearly 90% within a median surveillance time of nearly 2 months and of nearly 83% within a median surveillance time of nearly 4 months.

- The prespecified interim analysis of the primary efficacy endpoint in the initial vaccination period, with a median surveillance time of 39.0 days, in support of EUA met prespecified study success criterion in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 89.3% (alpha adjusted 96.9% CI: 73.0, 95.8; $p < 0.0001$)
- The prespecified final analysis of the primary efficacy endpoint in the initial vaccination period, with a median surveillance time of 56.0 days, in support of EUA met prespecified study success criterion in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 89.7% (95% CI: 80.2, 94.6; $p < 0.001$).
- The final analysis of the primary efficacy endpoint in the initial vaccination period, with a median surveillance time of 101.0 days, in support of BLA met prespecified study success criterion in in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 82.6% (95% CI: 72.9, 88.8; $p < 0.0001$).

Subgroup analyses of the primary efficacy endpoint for subjects 18 to 64 years of age (84.5% [95% CI: 74.9, 90.5]), male and female subjects (80.1% [95% CI: 64.0, 89.0] and 85.1% [95% CI: 70.9, 92.4], respectively), White subjects (84.0% [95% CI: 74.1, 90.2]), and subjects of non-Hispanic or Latino origin (81.7% [95% CI: 71.2, 88.4]) resulted in VEs similar to that for the final analysis of the primary efficacy endpoint.

- Subgroup analyses of the primary efficacy endpoint for subjects with comorbidities (72.0% [95% CI: 49.2, 84.5] for the original definition and 73.1% [95% CI: 51.5, 85.1] for the revised definition) were lower than for subjects without comorbidities (89.0% [95% CI: 78.2, 94.5] for the original definition and 88.7% [95% CI: 77.5, 94.3] for the revised definition).
- Subgroup analyses of the primary efficacy endpoint for subjects with B.1.1.7 (Alpha) and non-B.1.1.7 variants of SARS-CoV-2 resulted in VEs of 79.1% (95% CI: 64.7, 87.6) and 89.4% (95% CI: 70.2, 96.2), respectively.

  - As an exploratory analysis, the VE for subjects co-administered seasonal influenza vaccine on Day 0 in the Seasonal Influenza Vaccine Sub study was 77.9% (95% CI: -3.2, 95.2).

- Relative VE of NVX-CoV2373 to protect against PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second vaccination in the blinded crossover vaccination period in serologically negative (to SARSCoV-2) adult subjects at baseline 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); relative VE of adult subjects irrespective of serostatus was 60.7% (95% CI: 45.6, 72.1).
- Durability of VE of NVX-CoV2373 to protect against PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second vaccination in either the initial or blinded crossover vaccination period waned over time, ranging from 86.5% (95% CI: 78.1, 91.7) at the start of the surveillance period to 28.9% (95% CI: -16.2, 56.4) at 6 months after the start of the surveillance period.

Key and other secondary efficacy endpoints were supportive of the final BLA analysis of the primary efficacy endpoint.

NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination in the initial vaccination period in in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 80.4% (95% CI: 67.9, 88.0) and results of subgroup analyses similar to those reported for the primary efficacy endpoint.

Relative VE of NVX-CoV2373 to protect against PCR-confirmed moderate or severe COVID-19 with onset from 7 days after second vaccination in the blinded crossover vaccination period in serologically negative (to SARS-CoV-2) adult subjects at baseline receiving deferred active vaccine (during the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 58.7% (95% CI: 40.7, 71.7).

Durability of VE of NVX-CoV2373 to protect against PCR-confirmed moderate or severe COVID-19 with onset from 7 days after second vaccination in either the initial or blinded crossover vaccination period waned over time, ranging from 84.8% (95% CI: 73.8, 91.1) at the start of the surveillance period to 29.6% (95% CI: -20.3, 58.8) at 6 months after the start of the surveillance period.

NVX-CoV2373 prevented PCR-confirmed symptomatic severe COVID-19 with onset from at least 7 days after second vaccination in the initial vaccination period in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 100% (95% CI: 16.4, 100.0) with all 6 cases of severe COVID-19 reported in the placebo group.

Relative VE of NVX-CoV2373 to protect against PCR-confirmed severe COVID-19 with onset from 7 days after second vaccination in the blinded crossover vaccination period in serologically negative (to SARS-CoV-2) adult subjects at baseline receiving deferred active vaccine (during

the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 30.1% (95% CI: -509.8, 94.2).

Durability of VE of NVX-CoV2373 to protect against PCR-confirmed moderate or severe COVID-19 with onset from 7 days after second vaccination in either the initial or blinded crossover vaccination period waned over time, from 93.0% (95% CI: -46.1, 99.7) at the start of the surveillance period to 30.1% (95% CI: -707.7, 93.9) at 6 months after the start of the surveillance period.

NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in the initial vaccination period in adult subjects regardless of baseline serostatus with a VE of 82.8% (95% CI: 73.2, 89.0).

NVX-CoV2373 prevented laboratory-confirmed (by PCR or N-protein serology) asymptomatic or symptomatic mild, moderate, or severe COVID-19 with onset from the day after the Day 35 Visit in the initial vaccination period in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 82.2% (95% CI: 73.2, 89.0).

NVX-CoV2373 prevented laboratory-confirmed (by N-protein serology) asymptomatic SARS-CoV-2 infection detected from the day after the Day 35 Visit in the initial vaccination period COVID-19 in serologically negative (to SARS-CoV-2) adult subjects with a VE of 80.1% (95% CI: 60.8, 89.9).

Exploratory efficacy endpoints analysing VE from the start of first vaccination were also supportive of the final BLA analysis of the primary efficacy endpoint.

- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset after first vaccination in adult subjects regardless of baseline serostatus or receipt of second vaccination with a VE of 69.2% (95% CI: 58.4, 77.1; p-value < 0.001%) with an LBCI > 30% meeting the prespecified study success criterion and results of subgroup analyses similar to those reported for the primary and secondary efficacy endpoints.
- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from 7, 10, and 14 days after first vaccination in adult subjects regardless of baseline serostatus or receipt of second vaccination with VEs of 73.3% (95% CI: 63.2, 80.6), 77.0% (95% CI: 67.5, 83.7), and 80.1% (95% CI: 71.0, 86.3).
- NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset after first vaccination in adult subjects regardless of baseline serostatus or receipt of second vaccination with a VE of 65.3% (95% CI: 51.7, 75.1) and results of subgroup analyses similar to those reported for the primary and secondary efficacy endpoints.
- NVX-CoV2373 prevented PCR-confirmed symptomatic severe COVID-19 with onset after first vaccination in adult subjects regardless of baseline serostatus or receipt of second vaccination with a VE of 75.0% (95% CI: -17.9, 94.7).
- NVX-CoV2373 prevented laboratory-confirmed (by PCR or N-protein serology) asymptomatic or symptomatic mild, moderate, or severe COVID-19 with onset from first

vaccination in the initial vaccination period in adult subjects regardless of baseline serostatus or receipt of second vaccination with a VE of 68.8% (95% CI: 60.9, 75.3).

- NVX-CoV2373 prevented laboratory-confirmed (by N-protein serology to SARS-CoV-2) asymptomatic SARS-CoV-2 infection detected from first vaccination in the initial vaccination period in adult subjects regardless of baseline serostatus or receipt of second vaccination with a VE of 68.1% (95% CI: 45.8, 81.3).
- After first vaccination in the initial vaccination period, VEs of NVX-CoV2373 to prevent symptomatic mild, moderate, or severe COVID-19 increased from 69.2% (95% CI: 58.4, 77.6) after first vaccination to 81.6% (95% CI: 71.9, 88.4) at 7 days after second vaccination in adult subjects irrespective of use of prohibited medications, actual serostatus, or compliance with the vaccination schedule. These findings support the strong immune response of NVX-CoV2373 against symptomatic COVID-19.
- Relative VE of NVX-CoV2373 to protect against PCR-confirmed mild, moderate, or severe COVID19 with onset after the first vaccination in the blinded crossover vaccination period in adult subjects irrespective of use of prohibited medications, actual serostatus, or compliance with the vaccination schedule receiving deferred active vaccine (during the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 60.7% (95% CI: 46.8, 71.8).
- Relative VE of NVX-CoV2373 to protect against PCR-confirmed moderate or severe COVID19 with onset after the first vaccination in the blinded crossover vaccination period in adult subjects irrespective of use of prohibited medications, actual serostatus, or compliance with the vaccination schedule receiving deferred active vaccine (during the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 58.4% (95% CI: 40.6, 71.3).
- Relative VE of NVX-CoV2373 to protect against PCR-confirmed severe COVID19 with onset after the first vaccination in the blinded crossover vaccination period in adult subjects irrespective of use of prohibited medications, actual serostatus, or compliance with the vaccination schedule receiving deferred active vaccine (during the blinded crossover vaccination period) to those who received immediate active vaccine (during the initial vaccination period) was 32.3% (95% CI: -491.3, 94.3).

Immunogenicity:

A two-dose regimen of NVX-CoV2373, administered 21 days apart in either the initial or crossover vaccination periods, induced robust immune responses (anti-S protein IgG and neutralising antibody) relative to placebo in adult subjects 18 to 84 years regardless of baseline serostatus. Immune response was higher in the younger adult cohort (18 to 64 years) than in the older adult cohort (65 to 84 years), but with similarly high SCRs. NVX-CoV2373 also induced cell-mediated responses that skewed toward a Th1-dominant cytokine pathway and demonstrated a fold-increase in S protein-specific IFN-γ-secreting cells which exceeded the 95th percentile of increases in placebo recipients.

- Serum Anti-S Protein IgG
  - At Day 35, in baseline seronegative (to SARS-CoV-2) subjects who received both doses of study vaccine in the initial vaccination period, serum anti-S protein IgG GMTs in NVX-CoV2373 recipients were increased relative to placebo recipients across all age groups (44,411.3 vs 113.7 EU/mL for subjects 18 to 84 years of age; 47,201.3 vs 113.7 EU/mL for subjects 18 to 64 years of age; and 37,892.8 vs 113.6 EU/mL for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across all age groups. SCRs in the NVX-CoV2373 groups were also markedly increased relative to placebo across all age groups (99.0% vs 0.7% for subjects 18 to 84 years of age; 99.0% vs 1.0% for subjects 18 to 64 years of age; and 99.1% vs 0% for subjects 65 to 84 years of age).
  - At Day 35, in subjects regardless of baseline serostatus who received both doses of study vaccine in the initial vaccination period, serum anti-S protein IgG GMTs in the NVX-CoV2373 recipients were markedly increased relative to placebo recipients across the age groups (46,781.8 vs 129.8 EU/mL for subjects 18 to 84 years of age; 50,799.5 vs 127.7 EU/mL for subjects 18 to 64 years of age; and 37,494.5 vs 135.9 EU/mL for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across all age groups. SCRs in the NVX-CoV2373 recipients also were markedly increased relative to placebo recipients in all age groups (98.9% vs 1.1% for subjects 18 to 84 years of age; 98.8% vs 1.5% for subjects 18 to 64 years of age; and 99.2% vs 0% for subjects 65 to 84 years of age).
  - At Day 35, in subjects stratified by baseline serostatus who received both doses of study vaccine in the initial vaccination period, serum anti-S protein IgG GMTs in the NVX-CoV2373 group were markedly increased relative to placebo for serologically negative (to SARS-CoV-2) adult subjects 18 to 84 years of age (44,338.0 vs 115.7 EU/mL, respectively); for serologically positive (to SARS-CoV-2) adult subjects 18 to 84 years of age (125,489.8 vs 1,756.9 EU/mL, respectively); and for adult subjects 18 to 84 years of age regardless of baseline serostatus (46,781.8 vs 129.8 EU/mL, respectively). Immune responses were highest in baseline seropositive (to SARS-CoV-2) subjects, but SCRs were similar by baseline serostatus. SCRs in the NVX-CoV2373 recipients also were markedly increased relative to placebo recipients in all baseline serostatus groups (99.1% vs 1.2% for serologically negative [to SARS-CoV-2] adult subjects; 98.8% vs 1.5% for serologically positive [to SARS-CoV-2] adult subjects; and 98.9% vs 1.1% for adult subjects regardless of baseline serostatus).
  - At Day 35, in baseline seronegative (to SARS-CoV-2) subjects who received both doses of study vaccine in the blinded crossover vaccination period, serum anti-S protein IgG GMTs in placebo to NVX-CoV2373 recipients were increased relative to NVX-CoV2373 to placebo recipients across all age groups (80,624.3 vs 5,627.2 EU/mL for subjects 18 to 84 years of age; 83,053.0 vs 5,537.2 EU/mL for subjects 18 to 64 years of age; and 59,414.1 vs 6,320.2 EU/mL for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across

all age groups. SCRs in the NVX-CoV2373 groups also were markedly increased relative to placebo across all age groups (99.4% vs 0% for subjects 18 to 84 years of age; 99.3% vs 1.0% for subjects 18 to 64 years of age; and 100.0% vs 0% for subjects 65 to 84 years of age).

- At Day 35, in subjects regardless of baseline serostatus who received both doses of study vaccine in the blinded crossover vaccination period, serum anti-S protein IgG GMTs in placebo to NVX-CoV2373 recipients were markedly increased relative to NVX-CoV2373 to placebo recipients across the age groups during the blinded crossover vaccination period (83,670.6 vs 6,256.3 EU/mL for subjects 18 to 84 years of age; 86,211.3 vs 6,248.4 EU/mL for subjects 18 to 64 years of age; and 60,813.5 vs 6,320.2 EU/mL for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across all age groups. SCRs in placebo to NVX-CoV2373 recipients also were markedly increased relative to NVX-CoV2373 to placebo recipients in all age groups (99.4% vs 0.0% for subjects 18 to 84 years of age; 99.4% vs 1.5% for subjects 18 to 64 years of age; and 100.0% vs 0% for subjects 65 to 84 years of age).
- At Day 35, in subjects stratified by baseline serostatus who received both doses of study vaccine in the blinded crossover vaccination period, serum anti-S protein IgG GMTs in the placebo to NVX-CoV2373 group were markedly increased relative to the NVX-CoV2373 to placebo group for serologically negative (to SARS-CoV-2) adult subjects 18 to 84 years of age (81,443.0 vs 5,848.2 EU/mL, respectively); for serologically positive (to SARS-CoV-2) adult subjects 18 to 84 years of age (130,599.4 vs 26,900.3 EU/mL, respectively); and for adult subjects 18 to 84 years of age regardless of baseline serostatus (83,670.6 vs 6,256.3 EU/mL, respectively). Immune responses were highest in baseline seropositive (to SARS-CoV-2) subjects, but SCRs were similar by baseline serostatus. SCRs in placebo to NVX-CoV2373 recipients also were markedly increased relative to NVX-CoV2373 to placebo recipients in all baseline serostatus groups (99.4% vs 0.0% for serologically negative [to SARS-CoV-2] adult subjects 18 to 84 years of age; 99.4% vs 0.0% for serologically positive [to SARS-CoV-2] adult subjects 18 to 84 years of age; and 100.0% vs 0.0% for adult subjects 18 to 84 years of age regardless of baseline serostatus).

- Neutralising Antibody
  - At Day 35, in baseline seronegative (to SARS-CoV-2) subjects who received both doses of study vaccine in the initial crossover vaccination period, neutralising antibody GMTs in NVX-CoV2373 recipients were increased relative to placebo recipients across all age groups (1,132.7 vs 10.4, respectively, for subjects 18 to 84 years of age; 1,241.0 vs 10.5 for subjects 18 to 64 years of age; and 907.9 vs 10.1 for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across all age groups. SCRs in the NVX- CoV2373 groups were also markedly increased relative to placebo across all age groups (98.2% vs 0.5% for subjects

18 to 84 years of age; 98.1% vs 0.7% for subjects 18 to 64 years of age; and 98.2% vs 0% for subjects 65 to 84 years of age).

- At Day 35, in subjects regardless of baseline serostatus who received both doses of study vaccine in the initial vaccination period, neutralising antibody GMTs in the NVX-CoV2373 recipients were markedly increased relative to placebo recipients across the age groups (1,223.3 vs 11.3 for subjects 18 to 84 years of age; 1,357.2 vs 11.2 for subjects 18 to 64 years of age; and 940.6 vs 11.7 for subjects 65 to 84 years of age). Immune response was higher in the younger age cohort than the older age cohort, but SCRs were similar across all age groups. SCRs in the NVX-CoV2373 recipients also were markedly increased relative to placebo recipients in all age groups (98.3% vs 1.4% for subjects 18 to 84 years of age; 98.3% vs 1.6% for subjects 18 to 64 years of age; and 98.3% vs 0.9% for subjects 65 to 84 years of age).
- At Day 35, in subjects stratified by baseline serostatus who received both doses of study vaccine in the initial vaccination period, neutralising antibody GMTs in the NVXCoV2373 group were markedly increased relative to placebo for serologically negative (to SARS-CoV-2) adult subjects 18 to 84 years of age (1,134.3 vs 10.4, respectively); for serologically positive (to SARS-CoV-2) adult subjects 18 to 84 years of age (4,403.8 vs 62.0, respectively); and for adult subjects 18 to 84 years of age regardless of baseline serostatus (1,223.3 vs 11.3, respectively). Immune responses were highest in baseline seropositive (to SARS-CoV-2) subjects, but SCRs were similar by baseline serostatus. SCRs in the NVX-CoV2373 recipients also were markedly increased relative to placebo recipients in all baseline serostatus groups (98.2% vs 0.8% for serologically negative [to SARS-CoV-2] adult subjects 18 to 84 years of age; 100.0% vs 15.8% for serologically positive [to SARS-CoV-2] adult subjects 18 to 84 years of age; and 98.3% vs 1.4% for adult subjects 18 to 84 years of age regardless of B-cell-Mediated Immune Response

ICCS

- - Th1 (IFN-γ, TNF-α, and IL-2) and Th2 (IL-13 and IL-5) cytokine responses at Day 35 of the initial vaccination period were generally higher in NVX-CoV2373 recipients than placebo recipients, overall and by age group.
- A comparison of Th1 and Th2 cytokine levels among NVX-CoV2373 recipients showed higher levels of Th1 cytokines, in particular IFNγ and TNFα, than Th2 cytokine levels. These findings support a Th1predominant pathway for NVX-CoV2373.

ELISpot Assay

- In the NVX-CoV2373 group, strong induction of T cells secreting IFN-γ occurred in response to peptide pools reflecting the full length of the SARS-CoV-2 spike protein, and to its N-terminal and C-terminal portions, with geometric mean fold-rises of 16.5, 14.2, and 8.4-fold, respectively.

- Rises in T-cell counts responsive to the membrane or nucleocapsid proteins were essentially absent, and equivalent in the active and placebo groups. This is consistent with the absence of these antigens in the vaccine.
- C-terminal peptide pool sequences elicited somewhat lesser responses than the full length or N-terminal peptide pools, but with a similar pattern.
- The amplitude of T-cell responses was generally lower in vaccinated subjects ≥ 65 years of age.
- Seasonal Influenza Vaccine Sub-study
    - Co-administration of a licensed seasonal influenza vaccine on Day 0 with a two-dose regimen of NVX-CoV2373, administered on Days 0 and 21 of the initial vaccination period, showed that there was no statistically significant effect of NVX-CoV2373 on HAI GMTs of 4 influenza strains.
    - In a post-hoc analysis, NVX-CoV2373 elicited a robust anti-S protein response versus placebo at Day 35 that was diminished by approximately 30% in comparison to subjects not administered an influenza vaccine on Day 0 (44,411.3 vs 31,395.6 EU/mL [29.3% lower] for subjects 18 to 84 years of age; 47,201.3 vs 31,516.9 EU/mL [33.2% lower] for subjects 18 to 64 years of age; and 37,892.8 vs 29,215.4 EU/mL [22.9%] for subjects 65 to 84 years of age); however, SCRs remained similar (99.0% vs 97.7% for subjects 18 to 84 years of age; 99.0% vs 97.6% for subjects 18 to 64 years of age; and 99.1% vs 100.0% for subjects 65 to 84 years of age). A direct comparison to subjects not immunised with an influenza vaccine could not be made for the 65- to 84-year-old age stratum within the sub-study, although anti-S protein IgG response was vigorous in this group.

Safety:

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant), administered 21 days apart, was well tolerated in medically stable adult subjects 18 to 84 years of age with over 94% of subjects receiving both doses of NVX-CoV2373.

- Solicited Local TEAEs
    - There were higher frequencies of solicited local TEAEs within the first 7 days of each vaccination among NVX-CoV2373 recipients than among placebo recipients, with higher frequencies, intensity, and duration reported following second vaccination, but most subjects reported Grade 1 or Grade 2 events that were of short duration.
    - In the NVX-CoV2373 group, the frequency, intensity, and duration of solicited local TEAEs increased after second vaccination relative to the first vaccination but the study vaccine remained well tolerated.
    - The majority of subjects in the NVX-CoV2373 group reported Grade 1 events following first vaccination and Grade 1 or Grade 2 events following second vaccination.

- Frequencies of Grade 3 events were low but occurred at a higher frequency in the NVX-CoV2373 group than in the placebo group. No Grade 4 events were reported in either study vaccine group.
- After dose 2, tenderness and pain were the most frequent solicited local TEAEs in the 2 study vaccine groups, with 924 (76.7%) and 968 (80.4%) subjects, respectively, in the NVX-CoV2373 group and 164 (14.0%) and 200 (17.1%) subjects in the placebo group. Grade 3 tenderness and pain were reported in 49 (4.1%) and 1 (< 0.1%) subjects in the NVX-CoV2373 group and 11 (0.9%) and 0 subject in the placebo group. Median durations of tenderness and pain were 3.0 and 1.0 days in the NVX-CoV2373 group and 1.0 day in the placebo group.
- Across the 2 age strata, subjects in the older age cohort (65 to 84 years of age) reported a lower frequency and intensity of solicited local TEAEs than subjects in the younger age cohort (18 to 64 years of age).

- Solicited Systemic TEAEs
  - There were higher frequencies of solicited systemic TEAEs within the first 7 days of each vaccination among NVX-CoV2373 recipients than among placebo recipients, with higher frequencies and intensities reported following second vaccination, but most subjects reported Grade 1 or Grade 2 events that were of short duration.
  - Overall, there were higher frequencies of solicited systemic TEAEs among NVX-CoV2373 recipients than among placebo recipients following each vaccination overall and in each age cohort. In the NVX-CoV2373 group, the frequency, intensity, and duration of solicited systemic TEAEs increased after second vaccination relative to the first vaccination but the study vaccine remained well tolerated.
  - Following first vaccination in subjects 18 to 84 years of age, there was a higher frequency of solicited systemic TEAEs in the NVX-CoV2373 group (47.6%) than in the placebo group (37.9%), with the majority of subjects in the NVXCoV2373 (382 [62.6%] of 610) and placebo (287 [59.5%] of 482) groups reporting Grade 1 events. Few subjects reported Grade 3 events, with the same frequency (1.3%) of events in each study vaccine group. Two (0.2%) subjects in the NVX-CoV2373 group and no subject in the placebo group reported Grade 4 events. Headache, fatigue, and muscle pain were the most frequently solicited systemic TEAEs.
  - The most frequent solicited systemic TEAEs following each vaccination were headache, fatigue, and muscle pain, which had a median duration of ≤ 1.5 days following first vaccination and a median duration of ≤ 2.0 days following second vaccination.
  - Across the 2 age strata, subjects in the older age cohort (65 to 84 years of age) reported a lower frequency and intensity of solicited systemic TEAEs than subjects in the younger age cohort (18 to 64 years of age).
  - Similar patterns of response in terms of frequency and intensity were seen in the 2 subset analyses in subjects 18 to 84 years of age, with higher frequencies of solicited systemic

TEAEs reported in both NVX-CoV2373 and placebo recipients in the Seasonal Influenza Vaccine Sub-study. Despite these higher frequencies, the majority of subjects in the NVX-CoV2373 group reported Grade 1 events following first vaccination and Grade 1 or Grade 2 events following second vaccination.

- Unsolicited TEAEs
  - There were higher frequencies of subjects 18 to 84 years of age reporting unsolicited TEAEs and treatment-related TEAEs within the 49 days after first vaccination in the NVX-CoV2373 group (42.3% and 28.2%, respectively) than in the placebo group (26.6% and 9.7%), but most TEAEs and treatment-related TEAEs were mild or moderate in severity.
  - Severe TEAEs occurred in 122 (1.6%) subjects in the NVX-CoV2373 group and 99 (1.3%) subjects in the placebo group, with severe treatment-related TEAEs reported in 43 (0.6%) subjects in the NVX-CoV2373 group and 12 (0.2%) subjects in the placebo group.
  - Three (< 0.1%) subjects died in the placebo-controlled portion of the study, with 2 deaths (COVID-19 pneumonia and morphine and fentanyl toxicity) in the NVX-CoV2373 group and 1 death (sepsis related to COVID-19) in the placebo group; all 3 deaths were assessed as not related to study vaccine. One subject in the NVX-CoV2373 group died during the crossover period of cardiac arrest, which was determined to be not related to the study vaccine.
  - One TEAE (myocarditis) in the NVX-CoV2373 group assessed as related by the investigator (but not by the sponsor) to study vaccine.
  - Other unsolicited TEAEs (TEAEs leading to vaccination and study discontinuation, MAAEs, PIMMCs, and AESIs relevant to COVID-19) were reported at similar frequencies among both NVX-CoV2373 and placebo recipients.
  - Unsolicited TEAE profiles were similar between the 2 age strata for both the NVX- CoV2373 and placebo groups.

7.2.6 Study 2019nCoV-307

Study **2019nCoV-307** randomized, observer-blinded, Phase 3 study to compare the immunogenicity of 3 lots of NVX-CoV2373 in adults met the primary endpoint by demonstrating equal immunogenicity between the 3 lots of NVX-CoV2373. Additionally, immunogenicity increased in all subjects from Day 1 to Day 29.

Safety Conclusions:

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

- Serious TEAEs occurred in 2 (0.2%) subjects and included non-cardiac chest pain and Escherichia infection, neither of which were considered related to study vaccine. No deaths occurred in the study, and no TEAEs led to study discontinuation.
- A total of 39 (4.3%) subjects reported at least one unsolicited and medically attended TEAE. The most common TEAE (PT) was COVID-19 (14, 1.5%); the incidences for all other TEAEs were less than 0.5% each. Vaccine-related TEAEs occurred in 6 (0.7%) subjects, one of which were severe. Severe TEAEs occurred in 2 (0.2%) subjects, including post procedural infection and non-cardiac chest pain, neither of which were considered related to study vaccine. This study did not collect non-MAAEs.
- No AESIs, PIMMCs, or TEAEs representing complications specific to COVID-19 were reported during the study.

Overall Conclusion

NVX-CoV2373 showed equivalent immunogenicity across manufacturing lots, as measured by IgG and NAb responses to the vaccine-based prototype strain. No new safety signals were identified. NVX-CoV2373 was immunogenic regardless of whether it was used as a first booster or later booster dose, and whether it followed earlier doses of NVX-CoV2373 or other authorized vaccines. The broad cross-reactivity of induced antibodies with Omicron subvariants suggests that protection afforded by boosting with the prototype NVX-CoV2373 vaccine may extend to more recently evolved variants.

Study **2019nCoV-501** assessed efficacy, immunogenicity, and safety (excluding reactogenicity data) were assessed through approximately Month 12 after the second vaccination of the primary vaccination series (i.e., Day 386) and included data segregated into the precrossover and booster/crossover vaccination periods.

Efficacy:

A two-dose regimen of NVX-CoV2373 (5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant), administered 21 days apart (post-crossover) (with onset from at least 7 days after second booster/crossover vaccination [i.e, Day 229]) prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 at Month 12 (i.e., Day 386 [EoS]) analyzed overall in serologically naïve healthy adult HIV negative subjects and medically stable Persons Living with HIV (PLWH).

VE for prevention of PCR confirmed symptomatic mild, moderate, or severe COVID-19 decreased initially from Day 35 through Month 6 (i.e., Day 201) in the pre-crossover vaccination period and then increased from Month 6 through Day 386 (EoS) following booster/post-crossover vaccinations in the booster/post-crossover vaccination period analyzed overall in serologically naïve healthy adult HIV-negative subjects and medically stable PLWH.

- Through Month 12 (i.e., Day 386 [EoS]) in all subjects seronegative (to SARSCoV-2) at baseline, analyzed from 7 days after second booster/crossover vaccination (i.e., Day 229), VE of NVX-CoV2373 to booster in prevention of mild, moderate, or severe COVID19 at was 57.4% (95% CI: 16.3, 78.3) (p=0.013).

- Through Month 6 (pre-crossover) (i.e., Day 201) in all subjects, seronegative (to SARS-CoV-2) at baseline, analyzed from 7 days after second vaccination (pre-crossover) (i.e., Day 28), VE of NVX-CoV2373 in prevention of mild, moderate, or severe COVID19 was 37.4% (95% CI: 19.6, 51.2).
- Through Day 35 (pre-crossover) in all subjects seronegative (to SARSCoV-2) at baseline, analyzed from 7 days after second vaccination (pre-crossover) (i.e., Day 28), VE of NVX-CoV2373 in prevention of mild, moderate, or severe COVID19 was 48.6% (95% CI: 28.4, 63.1).
- Through Month 12 (i.e., Day 386 [EoS]) in HIV-negative subjects seronegative (to SARS-CoV-2) at baseline, analyzed from 7 days after second booster/crossover vaccination (i.e., Day 229), VE of NVX-CoV2373 to booster in prevention of mild, moderate, or severe COVID19 was 56.4% (95% CI: 11.9, 78.4) (p=0.021).
- Through Month 6 (pre-crossover) (i.e., Day 201) in HIV-negative subjects seronegative (to SARS-CoV-2) at baseline, analyzed from 7 days after second vaccination (pre-crossover) (i.e., Day 28), VE of NVX-CoV2373 to booster in prevention of mild, moderate, or severe COVID19 was 39.3% (95% CI: 21.2, 53.3).
- Through Day 35 (pre-crossover) in HIV-negative subjects seronegative (to SARSCoV-2) at baseline, analyzed from 7 days after second vaccination (precrossover) (i.e., Day 28), VE of NVX-CoV2373 in prevention of mild, moderate, or severe COVID19 was 55.4% (95% CI: 35.9, 68.9).
- Through Month 12 (i.e., Day 386 [EoS]) in PLWH seronegative (to SARS-CoV-2) at baseline, analyzed from 7 days after second booster/crossover vaccination (i.e., Day 229), VE of NVX-CoV2373 to booster in prevention of mild, moderate, or severe COVID19 was 74.3% (95% CI: -183.3, 97.7) (p=0.267).
- Through Month 6 (pre-crossover) (i.e., Day 201) in PLWH seronegative (to SARSCoV-2) at baseline, analyzed from 7 days after second vaccination (pre-crossover) (i.e., Day 28), VE of NVX-CoV2373 in prevention of mild, moderate, or severe COVID19 was 13.9% (95% CI: -90.4, 61.0).
- Through Day 35 (pre-crossover) in PLWH seronegative (to SARS-CoV-2) at baseline, analyzed from 7 days after second vaccination (pre-crossover) (i.e., Day 28), VE of NVX-CoV2373 in prevention of mild, moderate, or severe COVID19 was 35.4% (95% CI: -236.9, 45.6).
- VE through Month 12 in serologically naïve HIV-negative subjects (pre-crossover) analyzed from Day 28, VE of NVX-CoV2373 in prevention of symptomatic mild, moderate, or severe COVID-19 (beta variant) was 50.4% (95% CI: 29.7, 64.9).
- No cases of severe COVID19 were reported in any treatment group during the booster/crossover period.

Immunogenicity:

A 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 (EoS) in healthy HIV-negative South African subjects ≥ 18 to < 85 years of age and medically stable PLWH ≥ 18 to < 65 years of age.

Anti-S IgG

Cumulative Immune Responses – Baseline Day 0 (Entire Study)

- An initial robust anti-S IgG response was reached at Day 35 following a 2-dose primary vaccination series (pre-crossover), with GMFRs referencing baseline [Day 0] ranging from 92.3 to 164.2 for all subjects regardless of HIV status or baseline serostatus.
- Through Day 236 (35 days following third [booster] post-crossover vaccination), anti-S IgG responses were approximately 2.2fold higher to the peak response reached initially at Day 35 (pre-crossover) following the 2-dose primary vaccination series, for all subjects regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 92.3 to 164.2 at Day 35 (pre-crossover) and from 207.0 to 355.7 at Day 236 (post-crossover).
- Anti-S IgG responses declined to a greater extent from Day 35 following the 2-dose primary vaccination series through Month 6 (180 days following second vaccination [pre-crossover]) then they did from Day 236 (35 days following third [booster] post-crossover vaccination) through Day 386 (185 days following third [booster] post-crossover vaccination [EoS]) for all subjects regardless of HIV status or baseline serostatus.
- From Day 35 through Month 6 anti-S IgG responses declined between 6.3- and 8.0fold for all subjects, regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 92.3 to 164.2 at Day 35 [pre-crossover] and from 14.6 to 20.6 at Month 6 [Day 201 pre-crossover]).
- From Day 236 (post-crossover) through Day 386 (EoS) anti-S IgG responses declined 2.7-fold for all subjects regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 207.0 to 355.7 at Day 236 [post-crossover] and from 77.4 to 134.1 at Day 386 [EoS]).
- SCRs (≥ 4-fold increase) at Day 35 (pre crossover) ranged from 97.0% to 98.6%, at Month 6 (Day 201 pre-crossover) ranged from 83.2% to 88.3%, at Day 236 (post crossover) ranged from 99.2% to 100.0%, and at Day 386 (EoS) ranged from 96.2% to 98.1% for all subjects, regardless of HIV status or baseline serostatus.

Immune Responses From Month 6 Through Month 12 – Baseline Month 6 (Post-Crossover)

- Anti-S IgG antibody GMT levels for NVX-CoV2373 to booster and placebo to NVXCoV2373 increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for all subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG post-crossover booster vaccination response for the NVXCoV2373 to booster population declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than that of placebo to NVX-CoV2373 (6.1fold) in all subjects

seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 31.9 and 12.6 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 408.5 and 66.9, respectively).

- The initial robust anti-S IgG post-crossover booster vaccination response for the NVXCoV2373 to booster population declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.1fold) in all subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.3 and 4.1 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 107.9 and 26.4, respectively).
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVXCoV2373 (4.7-fold) in all subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 17.1 and 6.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 175.7 and 37.3, respectively).
- Anti-S IgG antibody GMT levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) for HIV-negative subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (6.1-fold) in HIV-negative subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 32.1 and 12.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 413.1 and 67.3, respectively).
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than that of placebo to NVX-CoV2373 (4.1-fold) in HIV-negative subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.3 and 4.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 111.1 and 27.2, respectively).
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.7-fold) in HIV-negative subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 17.4 and 7.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 182.7 and 38.5, respectively).
- Anti-S IgG antibody GMT levels for NVX-CoV2373 to booster and placebo to NVXCoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) for PLWH seronegative or seropositive at baseline, or regardless of baseline serostatus.

- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.8-fold) from Day 236 through Day 386 (EoS) than that of placebo to NVXCoV2373 (5.5-fold) in PLWH seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-crossover] of 29.4 and 10.6 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 330.2 and 60.1, respectively).
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.8-fold) from Day 236 through Day 386 (EoS) than that of placebo to NVXCoV2373 (4.1-fold) in PLWH seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-crossover] of 10.0 and 3.6 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 83.4 and 20.3, respectively).
- The initial robust anti-S IgG peak response for NVX-CoV2373 to booster declined to a lesser extent (2.6-fold) from Day 236 through Day 386 (EoS) than that of placebo to NVXCoV2373 (4.3-fold) in PLWH regardless of baseline serostatus (GMFRs for NVXCoV2373 to booster referencing Month 6 [Baseline – Post-crossover] of 13.8 and 5.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 113.0 and 26.2, respectively).
- SCRs (≥ 4-fold increase) at Day 236 ranged from 75.6% to 100.0% for NVX-CoV2373 to booster and from 97.6% to 100.0% for placebo to NVX-CoV2373 across all categories.
- SCRs (≥ 4-fold increase) at Day 386 (EoS) ranged from 40.0% to 88.4% for NVXCoV2373 to booster and from 92.3% to 100.0% for placebo to NVX-CoV2373 across all categories.

Immune Responses (Beta Variant) From Month 6 Through Month 12 – Baseline Month 6 (Post-Crossover)

- Anti-S IgG (beta variant) antibody GMT levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for all subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG (beta variant) post-crossover booster vaccination response for the NVX-CoV2373 to booster population declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.7fold) in all subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 29.3 and 11.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 280.1 and 59.7, respectively).
- The initial robust anti-S IgG (beta variant) post-crossover booster vaccination response for the NVX-CoV2373 to booster population declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.9fold) in all subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.3 and 4.3 at Day 236 and Day 386, respectively, and for

placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 94.8 and 24.5, respectively).

- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.1-fold) in all subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 16.4 and 6.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 140.8 and 34.1, respectively).
- Anti-S IgG (beta variant) antibody levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) for HIV-negative subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.7-fold) in HIV-negative subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 29.3 and 12.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 278.1 and 59.8, respectively).
- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.8-fold) in HIV-negative subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.4 and 4.3 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 97.9 and 25.5, respectively).
- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.1-fold) in HIV-negative subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 16.8 and 7.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 145.3 and 35.4, respectively).
- Anti-S IgG (beta variant) antibody levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) for PLWH seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (3.0-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (5.6-fold) in PLWH seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 28.0 and 9.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 323.9 and 57.8, respectively).
- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.6-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.1-fold) in PLWH seropositive at baseline (GMFRs for NVX-

CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 9.6 and 3.7 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 71.0 and 17.5, respectively).

- The initial robust anti-S IgG (beta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.6-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.3-fold) in PLWH regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 13.2 and 5.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 99.2 and 23.2, respectively).
- SCRs (≥ 4-fold increase) at Day 236 ranged from 75.6% to 94.1% for NVX-CoV2373 to booster and from 94.8% to 100.0% for placebo to NVX-CoV2373 across all categories.
- SCRs (≥ 4-fold increase) at Day 386 (EoS) ranged from 31.4% to 85.7% for NVXCoV2373 to booster and from 90.2% to 100.0% for placebo to NVX-CoV2373 across all categories.

Immune Responses (Delta Variant) From Month 6 Through Month 12 – Baseline Month 6 (Post-Crossover)

- Anti-S IgG (delta variant) antibody levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for all subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG (delta variant) post-crossover booster vaccination response for the NVX-CoV2373 to booster population declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.3fold) in all subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 28.8 and 11.5 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 239.7 and 55.6, respectively).
- The initial robust anti-S IgG (delta variant) post-crossover booster vaccination response for the NVX-CoV2373 to booster population declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.9-fold) in all subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.0 and 4.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 93.4 and 24.0, respectively).
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.0-fold) in all subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 16.1 and 6.5 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 131.8 and 32.8, respectively).
- Anti-S IgG (delta variant) antibody levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236

and declined thereafter through Day 386 (EoS) for HIV-negative subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.

- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.3-fold) in HIV-negative subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 28.9 and 12.0 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 238.5 and 55.8, respectively).
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.9-fold) in HIV-negative subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.1 and 4.1 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 95.7 and 24.8, respectively).
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.4-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.0-fold) in HIV-negative subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 16.4 and 6.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 135.2 and 33.8, respectively).
- Anti-S IgG (delta variant) antibody levels for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) for PLWH seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (4.1-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (5.1-fold) in PLWH seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 26.7 and 6.5 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 263.6 and 51.3, respectively).
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (2.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.2-fold) in PLWH seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 9.3 and 3.3 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 75.5 and 18.1, respectively).
- The initial robust anti-S IgG (delta variant) peak response for NVX-CoV2373 to booster declined to a lesser extent (3.1-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.3-fold) in PLWH regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 12.7 and 4.1 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 99.4 and 23.2, respectively).

- SCRs (≥ 4-fold increase) at Day 236 ranged from 73.2% to 91.8% for NVX-CoV2373 to booster and from 97.6% to 100.0% for placebo to NVX-CoV2373 across all categories.
- SCRs (≥ 4-fold increase) at Day 386 (EoS) ranged from 31.4% to 84.5% for NVXCoV2373 to booster and from 90.2% to 100.0% for placebo to NVX-CoV2373 across all categories.

Human Angiotensin-Converting Enzyme Receptor Binding Inhibition

Cumulative Immune Responses – Baseline Day 0 (Entire Study)

- An initial robust hACE2 receptor binding inhibition was reached at Day 35 following a 2-dose primary vaccination series (precrossover), with GMFRs referencing baseline [Day 0] ranging from 15.1 to 23.0 for all subjects regardless of HIV status or baseline serostatus.
- Through Day 236 (35 days following third [booster] post-crossover vaccination), hACE2 receptor binding inhibition increased up to 3-fold relative to the peak response reached initially at Day 35 (pre-crossover) following the 2-dose primary vaccination series, for all subjects regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 15.1 to 23.0 at Day 35 (pre-crossover) and from 45.4 to 60.0 at Day 236 (post-crossover).
- hACE2 receptor binding inhibition declined to a greater extent from Day 35 following the 2-dose primary vaccination series through Month 6 (180 days following second vaccination [precrossover]) then it did from Day 236 (35 days following third [booster] post-crossover vaccination) through Day 386 (185 days following third [booster] post-crossover vaccination [EoS]) for all subjects regardless of HIV status or baseline serostatus.
- From Day 35 through Month 6 hACE2 receptor binding inhibition declined between 5- and 8.1-fold for all subjects, regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 15.1 to 23.0 at Day 35 [pre-crossover] and from 2.8 to 3.0 at Month 6 [Day 201 pre-crossover]).
- From Day 236 (post-crossover) through Day 386 (EoS) hACE2 receptor binding inhibition declined between 2.6 and 3.1-fold for all subjects, regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 45.4 to 60.0 at Day 236 [post-crossover] and from 14.8 to 23.2 at Day 386 [EoS]).
- SCRs (≥ 4-fold increase) at Day 35 (precrossover) ranged from 81.8% to 89.7%, at Month 6 (Day 201 pre-crossover) ranged from 33.3% to 45.8%, at Day 236 (post-crossover) ranged from 98.3% to 98.7%, and at Day 386 (EoS) ranged from 92.3% to 95.0% for all subjects, regardless of HIV status or baseline serostatus.

Immune Responses From Month 6 Through Month 12 – Baseline Month 6 (Post-Crossover)

- hACE2 receptor binding inhibition for NVX-CoV2373 to booster and placebo to NVXCoV2373 increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for all subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.

- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.7-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (8.6-fold) in all subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 44.10 and 16.37 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 40.53 and 4.69, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.7-fold) in all subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.04 and 3.97 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 53.71 and 11.42, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.6-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (5.9-fold) in all subjects regardless of baseline serostatus – as determined by a comparison of the ratio of GMFRs at these time points (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 19.47 and 7.53 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 48.46 and 8.20, respectively).
- hACE2 receptor binding inhibition for NVX-CoV2373 to booster and placebo to NVXCoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for HIV-negative subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.6-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (10.0-fold) in HIV-negative subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 45.76 and 17.32 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 41.11 and 4.61, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.6-fold) in HIV-negative subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 10.10 and 4.11 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 54.88 and 11.91, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (6.0-fold) in HIV-negative subjects regardless of baseline serostatus – as determined by a comparison of the ratio of GMFRs at these time points (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 20.29 and 8.01 at Day 236 and Day 386, respectively, and for placebo to NVXCoV2373 referencing Month 6 [Baseline – Post-Crossover] of 49.21 and 8.27, respectively).

- hACE2 receptor binding inhibition for NVX-CoV2373 to booster and placebo to NVXCoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for PLWH seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (3.3-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.8-fold) in PLWH seronegative at baseline (GMFRs for NVXCoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 23.36 and 6.98 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 30.74 and 6.35, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (3.3-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (5.6-fold) in PLWH seropositive at baseline (GMFRs for NVXCoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 9.52 and 2.92 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 44.10 and 7.89, respectively).
- The initial robust hACE2 receptor binding inhibition for NVX-CoV2373 to booster declined to a lesser extent (3.2-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (5.4-fold) in PLWH regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 12.39 and 3.88 at Day 236 and Day 386, respectively, and for placebo to NVXCoV2373 referencing Month 6 [Baseline – Post-Crossover] of 40.67 and 7.50, respectively).
- SCRs (≥ 4-fold increase) at Day 236 ranged from 70.7% to 94.1% for NVX-CoV2373 to booster and from 92.3% to 97.8% for placebo to NVX-CoV2373 across all categories.
- SCRs (≥ 4-fold increase) at Day 386 (EoS) ranged from 31.4% to 87.2% for NVXCoV2373 to booster and from 44.0% to 76.9% for placebo to NVX-CoV2373 across all categories.

SARS-CoV-2 Wild-Type Virus Micro Neutralisation

Cumulative Immune Responses – Baseline Day 0 (Entire Study)

- An initial robust SARS-CoV-2 wild-type virus micro neutralisation response was reached at Day 35 following a 2-dose primary vaccination series (pre crossover), with GMFRs referencing baseline [Day 0] ranging from 33.1 to 64.6 for all subjects regardless of HIV status or baseline serostatus.
- Through Day 236 (35 days following third [booster] post crossover vaccination), SARSCoV-2 wild-type virus micro neutralisation increased approximately 2.8-fold relative to the peak response reached initially at Day 35 (pre-crossover) following the 2dose primary vaccination series, for all subjects regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 33.1 to 64.6 at Day 35 (pre-crossover) and from 100.4 to 178.0 at Day 236 (post crossover).
- SARSCoV-2 wild-type virus micro neutralisation declined to a greater extent from Day 35 following the 2-dose primary vaccination series through Month 6 (180 days following second

vaccination [pre crossover]) then they did from Day 236 (35 days following third [booster] post crossover vaccination) through Day 386 (185 days following third [booster] post crossover vaccination [EoS]) for all subjects regardless of HIV status or baseline serostatus.

- From Day 35 through Month 6 SARSCoV-2 wild-type virus micro neutralisation declined between 5.2- and 8.3-fold for all subjects, regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 33.1 to 64.6 at Day 35 [pre-crossover] and from 6.4 to 7.8 at Month 6 [Day 201 pre-crossover]).
- From Day 236 (post-crossover) through Day 386 (EoS) SARSCoV-2 wild-type virus micro neutralisation declined 1.9-fold for all subjects, regardless of HIV status or baseline serostatus (GMFRs referencing baseline [Day 0]) ranging from 100.4 to 178.0 at Day 236 [post-crossover] and from 53.1 to 94.7 at Day 386 [EoS]).
- SCRs (≥ 4-fold increase) at Day 35 (pre crossover) ranged from 96.0% to 97.5%, at Month 6 (Day 201 pre-crossover) ranged from 67.7% to 75.2%, at Day 236 (post-crossover) ranged from 99.5% to 100.0%, and at Day 386 (EoS) ranged from 97.8% to 100.0% for all subjects, regardless of HIV status or baseline serostatus.

Immune Responses From Month 6 Through Month 12 – Baseline Month 6 (Post-Crossover)

- SARSCoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster and placebo to NVX-CoV2373 increased from Month 6 (Baseline Post Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for all subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (2.0-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.6-fold) in all subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 57.0 and 29.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 128.3 and 27.8, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.2-fold) in all subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 9.0 and 5.1 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 82.2 and 25.8, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.6-fold) in all subjects regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 20.6 and 11.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 96.7 and 26.5, respectively).
- SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio

of GMFRs at these time points – for HIV negative subjects seronegative or seropositive at baseline, or regardless of baseline serostatus.

- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.9-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (4.7-fold) in HIV-negative subjects seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 58.3 and 30.4 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 128.4 and 27.1, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.2-fold) in HIV-negative subjects seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 9.3 and 5.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 81.7 and 25.9, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.7-fold) in HIV-negative subjects regardless of baseline serostatus GMFRs at these time points (GMFRs for NVXCoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 21.6 and 11.8 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 96.9 and 26.4, respectively).
- SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster and placebo to NVX-CoV2373 populations increased from Month 6 (Baseline Post-Crossover) to Day 236 and declined thereafter through Day 386 (EoS) – as determined by a comparison of the ratio of GMFRs at these time points – for PLWH seronegative or seropositive at baseline, or regardless of baseline serostatus.
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (2.5-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.0-fold) in PLWH seronegative at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 39.2 and 15.4 at Day 236 and Day 386, respectively, and for placebo to NVXCoV2373 referencing Month 6 [Baseline – Post-Crossover] of 128.0 and 42.7, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVXCoV2373 to booster declined to a lesser extent (1.8-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.5-fold) in PLWH seropositive at baseline (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 7.5 and 4.2 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 86.5 and 25.0, respectively).
- The initial robust SARS-CoV-2 wild-type virus micro neutralisation for NVX-CoV2373 to booster declined to a lesser extent (1.9-fold) from Day 236 through Day 386 (EoS) than did that for placebo to NVX-CoV2373 (3.3-fold) in PLWH regardless of baseline serostatus (GMFRs for NVX-CoV2373 to booster referencing Month 6 [Baseline – Post-Crossover] of 12.2 and 6.4 at Day 236 and Day 386, respectively, and for placebo to NVX-CoV2373 referencing Month 6 [Baseline – Post-Crossover] of 94.3 and 28.3, respectively).

- SCRs (≥ 4-fold increase) at Day 236 ranged from 67.5% to 100.0% for NVX-CoV2373 to booster and from 97.1% to 100.0% for placebo to NVX-CoV2373 across all categories.
- SCRs (≥ 4-fold increase) at Day 386 (EoS) ranged from 48.6% to 91.9% for NVXCoV2373 to booster and from 93.1% to 100.0% for placebo to NVX-CoV2373 across all categories.

Safety:

Through Month 12 (i.e., EoS), a two-dose regimen consisting 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 subjects ≥ 18 to < 85 years of age and medically stable PLWH ≥ 18 to < 65 years of age with 96.7% of subjects receiving both doses of NVX-CoV2373 (precrossover) and 97.8% of subjects receiving both doses of the post crossover – booster regimen.

Solicited Local Adverse Events

- The majority of subjects regardless of baseline serostatus to SARS-CoV-2, did not experience solicited local TEAEs following vaccination in either the initial vaccination period (Dose 1 [22.3%] and Dose 2 [20.0%]) or the crossover vaccination period (Dose 3 [2.7%] and Dose 4 [2.6%]); for Dose 3 and Dose 4 solicited local TEAEs were only recorded on a single day.
- The frequencies of subjects with solicited local TEAEs after Dose 1 and Dose 2 were similar and were higher for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 and after Dose 3 and Dose 4 were similar for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 and much lower than those for each treatment group than after Dose 1 and Dose 2.
- Few subjects reported Grade 3 events (i.e., severe) after Dose 1 (0.9%) and Dose 2 (1.4%) and the frequency of subjects with these events was higher for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 after Dose 1; no Grade 3 (i.e., severe) events were reported after Dose 3 or Dose 4.
- There were no reports of Grade 4 solicited local TEAEs.
- Pain and tenderness were the most frequently reported solicited local TEAEs after each vaccination across all subsets of subjects.
- Median durations of solicited local TEAEs were of short duration (generally ≤ 2.0 days).

Solicited Systemic Adverse Events

- The majority of subjects regardless of baseline serostatus to SARS-CoV-2, did not experience solicited systemic TEAEs following vaccination in either the initial vaccination period (Dose 1 [26.9%] and Dose 2 [20.9%]) or the crossover vaccination period (Dose 3 [0.8%] and Dose 4 [0.7%]); for Dose 3 and Dose 4 solicited systemic TEAEs were only recorded on a single day.
- The frequencies of subjects with solicited systemic TEAEs after Dose 1 and Dose 2 were higher for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 and after Dose 3 and Dose 4 were similar for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 and much lower than those for each treatment group than after Dose 1 and Dose 2.

- Few subjects reported Grade 3 events (i.e., severe) after Dose 1 (2.3%) and Dose 2 (2.9%) and the frequency of subjects with these events was higher for NVX-CoV2373 to booster versus placebo to NVX-CoV2373 after Dose 1; no Grade 3 (i.e., severe) events were reported after Dose 3 or Dose 4.
- There were no reports of Grade 4 solicited systemic TEAEs.
- Headache, fatigue, and muscle pain were the most frequently reported solicited systemic TEAEs after each vaccination.
- Median durations of solicited systemic TEAEs were generally of short duration (≤ 2.0 days)

Unsolicited Treatment-Emergent Adverse Events

- Through 35 days after first vaccination in the period over the entire study, among all subjects regardless of baseline serostatus, the annualised rate for subjects with unsolicited TEAEs was lower overall for NVX-CoV2373 (pre-crossover + post-crossover) (0.148 n/person-years [PY]) versus placebo (precrossover) (0.246 n/PY) (including for those with severe TEAEs, treatment-related TEAEs, treatment-emergent MAAEs, SAEs, any MAAEs, and AESI:suspected, probable, or confirmed related to COVID19 [for severe treatment-related TEAEs and any AESI:PIMMC, annualised rates of subjects with unsolicited TEAEs were the same for NVX-CoV2373 [precrossover + post-crossover] versus those for placebo [precrossover]). No treatment-related SAEs, treatment-related TEAEs leading to vaccination or study discontinuation, or treatment related AESI: PIMMC or AESI: suspected, probable, or confirmed related to COVID19 were reported for either treatment group.
- Through 35 days after first vaccination (i.e., precrossover), among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited TEAEs overall (NVXCoV2373 vs placebo, respectively) was similar for both treatment groups (13.7% vs 13.4%); the frequencies of subjects with unsolicited TEAEs (e.g., headache [3.1% vs 2.4%]) generally occurred at a < 1.0 percentage point higher frequency for NVXCoV2373 versus placebo.
- Through 35 days after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited TEAEs was higher overall for NVX-CoV2373 to booster (post-crossover) (0.8%) versus placebo to NVX-CoV2373 (post-crossover) (0.5%) with TEAEs mainly occurring due to reactogenicity (e.g., injection site pain [0.2% vs 0.0%]).
- Through EoS after first vaccination (pre-crossover) among all subjects regardless of baseline serostatus in the period over the entire study, the annualised rate of subjects with unsolicited TEAEs was lower overall for NVX-CoV2373 (precrossover + post-crossover) (0.198 n/PY) versus placebo (pre-crossover) (0.322 n/PY).
- Through EoS after third vaccination (post-crossover – booster) among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited TEAEs was slightly higher overall for NVX-CoV2373 (1.6%) versus placebo (1.4%) with the increased frequency mainly due to reactogenicity (e.g., injection site pain [0.2% vs 0.0%]).

Unsolicited TEAEs by Severity

- Through 35 days after first vaccination in the period over the entire study, among all subjects regardless of baseline serostatus, the annualised rate of subjects with unsolicited severe TEAEs was slightly lower overall for NVX-CoV2373 (precrossover + post-crossover) (0.009 n/PY) versus placebo (pre-crossover) (0.010 n/PY).
- Through 35 days after first vaccination (precrossover), among all subjects, unsolicited severe TEAEs were reported in 16 (0.7%) subjects in the NVX-CoV2373 group and 12 (0.5%) subjects in the placebo group, with BP increased and hypertension being the most frequently reported unsolicited severe TEAEs for NVX-CoV2373 in all subjects.
- Through 35 days after third vaccination (post-crossover – booster), unsolicited severe TEAEs for all subjects regardless of baseline serostatus were reported in 3 (0.2%) subjects for NVX-CoV2373 to booster and 2 (0.1%) subjects for placebo to NVXCoV2373 with injection site pain, injection site erythema, injection site induration, and renal failure (all < 0.1%) being the unsolicited severe TEAEs reported for NVXCoV2373.
- Through EoS after first vaccination (precrossover), among all subjects regardless of baseline serostatus, unsolicited severe TEAEs were reported in 30 (1.4%) subjects for NVX-CoV2373 and in 30 (1.4%) subjects for placebo with BP increased, hypertension, and death being the most frequently reported unsolicited severe TEAEs for NVXCoV2373.
- Through EoS after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, unsolicited severe TEAEs were reported in 11 (0.6%) subjects for NVX-CoV2373 to booster and 11 (0.6%) subjects for placebo to NVXCoV2373 with multiple injuries being the most frequently reported severe TEAE for NVX-CoV2373 to booster in all subjects.

Unsolicited Treatment-Related TEAEs

- Through 35 days after first vaccination in the period over the entire study, among all subjects regardless of baseline serostatus, the annualised rate of subjects with unsolicited treatment related TEAEs was lower overall for NVX-CoV2373 (precrossover + post-crossover) (0.045 n/PY) versus placebo (pre-crossover) (0.060 n/PY).
- Through 35 days after first vaccination (pre-crossover), among all subjects regardless of baseline serostatus, unsolicited treatment-related TEAEs were reported in 93 (4.2%) subjects for NVX-CoV2373 and in 72 (3.3%) subjects for placebo with the increased frequency of treatment-related TEAEs due mainly to reactogenicity (e.g., headache [1.9 % vs 1.3%], injection site pain [0.9% vs < 0.1%], myalgia [0.9% vs 0.6%]).
- Through 35 days after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited treatment-related TEAEs was higher overall for NVX-CoV2373 to booster (0.4%) versus placebo to NVX-CoV2373 (0.1%) with the increased frequency of treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain [0.2% vs 0.0%], injection site swelling [0.1% vs 0.0%]).
- Through EoS after first vaccination (precrossover), among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited treatment-related TEAEs was higher overall for NVX-CoV2373 (4.6%) versus placebo (3.4%) with the increased frequency of

treatment-related TEAEs due mainly to reactogenicity (e.g., headache [1.9% vs 1.3%], injection site pain [0.9% vs < 0.1%], myalgia [0.9% vs 0.6%], arthralgia [0.8% vs 0.4%]).

- Through EoS after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, the frequency of subjects with unsolicited treatment-related TEAEs was higher overall for NVX-CoV2373 to booster (0.4%) versus placebo to NVX-CoV2373 (0.1%) with increased frequency of treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain [0.2% vs 0.0%], injection site swelling [0.1% vs 0.0%], vaccination site lymphadenopathy [0.1% vs 0.0%], injection site erythema [< 0.1% vs 0.0%].

Unsolicited Treatment-Related Severe TEAEs

- Through 35 days after first vaccination in the period over the entire study, among all subjects regardless of baseline serostatus, the annualised rate of subjects with unsolicited severe treatment-related TEAEs was low and the same overall for NVX-CoV2373 (precrossover + post-crossover) (2 [< 0.001] n/PY) versus placebo (pre-crossover) (1 [< 0.001] n/PY) and included injection site pain (2 [< 0.001 n/PY]) and fatigue, malaise, headache, myalgia, arthralgia, nausea, and vomiting – all 1 (< 0.001 n/PY) for NVXCoV2373 (pre-crossover + post-crossover) and malaise (1 [< 0.001 n/PY]) for placebo (precrossover).
- Through 35 days after first vaccination (pre-crossover), among all subjects regardless of baseline serostatus, unsolicited severe treatment-related TEAEs were reported in 2 (< 0.1%) subjects overall for NVX-CoV2373 and in 1 (< 0.1%) subject for placebo with the unsolicited severe treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain (2 [< 0.1%]) and headache, fatigue, malaise, myalgia, arthralgia – all 1 [< 0.1%] for NVX-CoV2373) and malaise (1 [< 0.1%]) for placebo.
- Through 35 days after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, unsolicited severe treatment-related TEAEs were reported in 2 (0.1%) subjects overall for NVX-CoV2373 to booster and in 0 (0.0%) subjects for placebo to NVX-CoV2373 with the unsolicited severe treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain, injection site erythema, and injection site induration – all 1 ([< 0.1%]).
- Through EoS after first vaccination (pre-crossover), among all subjects regardless of baseline serostatus, unsolicited severe treatment-related TEAEs were reported in 2 (< 0.1%) subjects overall for NVX-CoV2373 and in 1 (< 0.1%) subject for placebo with the unsolicited severe treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain (2 [< 0.1%]) and headache, fatigue, malaise, myalgia, arthralgia, nausea, and vomiting – all 1 [< 0.1%] for NVX-CoV2373) and malaise (1 [< 0.1%]) for placebo.
- Through EoS after third vaccination (post-crossover – booster), among all subjects regardless of baseline serostatus, unsolicited severe treatment-related TEAEs were reported in 2 (0.1%) subjects overall for NVX-CoV2373 to booster and in 0 (0.0%) subjects for placebo to NVX-CoV2373 with the unsolicited severe treatment-related TEAEs due mainly to reactogenicity (e.g., injection site pain, injection site erythema, and injection site induration – all 1 [< 0.1%]

7.2.7 Study 2019nCoV-503

Study **2019nCoV-503** is a Phase 2/3 age de-escalating study to evaluate the safety and immunogenicity of SARS-CoV-2rS protein vaccine with Matrix-M adjuvant in children 6 months to < 12 years of age. An estimate of 280 subjects have been randomised of which 180 have received atleast one dose of NVX-CoV2373. No interim was planned as of DLP of this PBRER.

7.2.8 Study 2019nCoV-505

Study **2019nCoV-505** is a Phase 2, randomised, observer-blind study to evaluate the safety and immunogenicity of NVX-CoV2373 in people living with HIV. As of DLP, an estimate of 383 subjects have received NVX-CoV2373. No interim analysis was planned as of DLP of this PBRER.

7.2.9 Study 2019nCoV-311

Study **2019nCoV-311** is a Phase 3, randomised, observer-blind study to evaluate the safety and immunogenicity of two booster doses of the NVX-CoV2515 and Bivalent SARS-CoV-2 rS vaccines in adults previously vaccinated with other COVID-19 vaccines. As of DLP, 951 subjects were randomised and 317 of those have received NVX-CoV2373. No interim analysis was planned as of DLP of this PBRER.

7.3 Long-Term Follow-Up

NVX-sponsored CTs collects up to 2 years of follow-up data for enrolled subjects. No new safety information became available from NVX sponsored CTs as of DLP.

7.4 Other Therapeutic Use of Medicinal Product

During the reporting interval, one compassionate use study was ongoing in South Africa for Health Care Workers (HCW), as part of 2019nCoV-501 study. HCWs were followed for 6 months, and the last visit was a follow-up call to check on their overall health. A total of 99 HCWs were enrolled and 87 of them completed the study. No clinically relevant safety information was reported from the HCW compassionate use portion of the study. HCW data was collected outside of 2019nCoV-501 study.

7.5 New Safety Data Related to Fixed Combination Therapies

During the reporting interval, a Phase 1/2, randomised, observer-blind study (Study ID: **2019nCoV-ICC-E-101**) to evaluate the safety and immunogenicity of a fixed combination of quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy subjects ≥ 50 to ≤ 70 years of age was completed. No significant safety findings were observed following the end of study review.

8 FINDINGS FROM NON-INTERVENTIONAL SAFETY STUDIES

No safety findings were reported from any non-interventional safety studies, that would have an impact on benefit-risk profile of NVX-CoV2373.

During the reporting interval, one Post-Authorisation Safety Study (PASS) was ongoing, and no safety data or relevant safety information have been received that would impact the benefit-risk assessment of NVX-CoV2373.

As per EMA procedure, EMEA/H/C/005808/MEA/004, monthly feasibility assessments were planned for Study 2019nCoV-402. However, it was determined that a significant amount of data accrued since May 2022 was missing from the CPRD Arum database; therefore, the feasibility assessment cannot be conducted at this time. The next release of the CPRD Aurum database is planned for March 2023 and is expected to include complete data for approximately 200 practices. Future releases will include incremental updates of data from practices until the database has complete data from all practices.

Appendix 8 provides an overview of ongoing and planned safety studies.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

During the reporting interval, there were no relevant new safety observations identified from any other studies that would change the benefit-risk balance of NVX-CoV2373.

Appendix 7, Table 33 summarises details regarding ongoing studies managed by license partners and Table 34 summarises investigator-initiated trials.

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 9).

9.2.1 Results and Discussion

105 ICSRs were retrieved for the interval (103 initial and 2 follow-up).

Cumulatively, 146 ICSRs were retrieved (61 males, 74 females, 11 individuals of unspecified sex, age range 9–85 years when reported). The 146 cumulative ICSRs included 189 AEs (1 serious and 188 non-serious). The most common PTs reported were Interchange of vaccine products (n=23), Vaccination error (n=21), Inappropriate schedule of product administration (n=17), Incomplete course of vaccination (n=17), Product administration error (n=16), Product administered to patient of inappropriate age (n=15), Expired product administered (n=10), and Product dose omission issue (n=10).

9.2.2 Conclusion

Cumulative evaluation of medication (vaccination) errors did not reveal any particular trend. No new potential safety issues were identified and no change to the benefit-risk assessment of NVX-CoV2373. Medication (vaccination) errors will continue to be monitored through routine pharmacovigilance activities.

10 NON-CLINICAL DATA

During the reporting interval, there were no safety findings from non-clinical studies that impacted the benefit-risk profile of NVX-CoV2373. Non-clinical studies performed until DLP of this PBRER have demonstrated that NVX-CoV2373 with Matrix-M adjuvant generated a robust and functional immune response eliciting neutralising antibodies against SARS-CoV-2, resulting in protective efficacy following live viral challenge across multiple species, including non-human primates. No adverse risks were identified in the non-clinical testing program as of DLP of this PBRER and the data supported the proposed dose and regimen for human use (i.e., 5 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant).

Table 13 provides summary of non-clinical studies either ongoing or completed during the reporting interval, for NVX-CoV2373.

Table 13: Summary of Non-Clinical Studies Evaluating NVX-CoV2373

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 (Ongoing)	OUHSC (in-life) Novavax (immune response) UMSOM (neutralisation) Non-GLP	Olive baboons (n = 2-3/group)	Immunisation 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.1.1351 SARS-CoV-2 rS BV2426 3 µg SARS-CoV-2 rS SA B.1.351 + 50 µg Matrix-M1 Administered on Day 318 (all animals) and Day 339 (1 – 2 animals/group) Boost with Prototype BV2373 and Omicron BA.1 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
702-134 Durability of SARS-CoV-2 rS Prototype and Omicron BA.1 Variant rS Induced Immunity in Baboons- One Year Study (Ongoing)	OUHSC (in-life) Novavax (immune response) Non-GLP	Olive baboons (n = 6/group)	Primary Series administered IM on Days 0 and 30 5 µg Prototype BV2373 or Omicron BA.1 BV2515 + 50 µg Matrix-M1 Booster administered IM on Day 150 (5 month) 5 µg Omicron BA.5 + 50 µg Matrix-M1 5 µg bivalent rS (2.5 µg Prototype BV2373 + 2.5 µg Omicron BA.5) + 50 µg Matrix M1	No safety findings

Table 13: Summary of Non-Clinical Studies Evaluating NVX-CoV2373

Study Number & Description (Status)	**Testing Facility (GLP Status)**	**Animals (N)**	**Study Design (Treatment Groups/ Administration/Endpoints)**	**Key Safety Conclusions**
702-149 Evaluation of 6 Month Booster Immunisation 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)	Day 0 and 21 Vaccination (IM) 5 µg SARS-CoV-2 rS BV2373 + 50 µg Matrix-M1 5 µg SARS-CoV-2 rS Delta + 50 µg Matrix-M1 6 Month Boost- 5 µg SARS-CoV-2 rS BV2373 + 50 µg Matrix M1 5 µg SARS-CoV-2 rS Omicron BA.1 + 50 µg Matrix M1 5 µg bivalent SARS-CoV-2 rS (2.5 µg Prototype BV2373 + 2.5 µg Omicron BA.1 BV2515) + 50 µg Matrix M1 Placebo	No safety findings
702-169 T Cell Responses of SARS-CoV-2 rS Omicron BA.2 Variant in Mice. (in-life 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
702-171 Immunogenicity of SARS-CoV-2 rS Prototype, Omicron BA.1, BA.5, and BA.2.12.1 Variants in Mice. (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

Table 13: Summary of Non-Clinical Studies Evaluating NVX-CoV2373

Study Number & Description (Status)	**Testing Facility (GLP Status)**	**Animals (N)**	**Study Design (Treatment Groups/ Administration/Endpoints)**	**Key Safety Conclusions**
702-172 T Cell Responses of SARS-CoV-2 rS Prototype, Omicron BA.5, BA.2.12.1 Variants in Mice. (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
702-173 Evaluation of Omicron BA.5 Vaccine in Rhesus (Ongoing)	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Day 0 and 21 Vaccination (IM) 5 µg SARS-CoV-2 rS BV2373 + 50 µg Matrix-M1 5 µg SARS-CoV-2 rS Omicron BA.5 + 50 µg Matrix-M1 Bivalent 5 µg (2.5 µg each rS) SARS-CoV-2 rS (Prototype BV2373 + Omicron BA.5) + 50 µg Matrix-M1	No safety findings
702-176 Immunogenicity of SARS-CoV-2 rS Omicron BA.1 GMP DP in mice. (In-life completed)	NLS (in-life) Novavax (immunogenicity) Non-GLP	BALB/c mice (n = 10/group)	0.1 µg and 0.5 µg Prototype BV2373 DP GMP, Omicron BA.1 DP GMP, or Omicron BA.1 Discovery 0.1 µg 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. (Ongoing)	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

11 LITERATURE

During the reporting interval, 13 literature articles were identified for NVX-CoV2373 and are discussed below.

Kumar 2022 published a systematic review and meta-analysis on Phase 3 randomised controlled trials that assessed efficacy of COVID-19 vaccines. Several vaccines approved for the prevention of COVID-19 had no head-to-head trials comparing their clinical efficacy performed. This network meta-analysis aimed to identify which of the existing approved vaccines, conferred maximum protection against COVID-19. A systematic literature search was conducted to identify Phase 3 randomised controlled clinical trials that evaluated efficacy of various COVID-19 vaccines. A total of 17 trials met inclusion criteria for the systematic review and network meta-analysis. These 17 studies included data from 361,386 subjects and assessed efficacy of 16 different COVID-19 vaccines. A forest plot for indirect comparison of the efficacy of COVID-19 vaccines was generated. Rankogram and 'P' scores were obtained to rank the vaccines based on the indirect evidence of their comparative efficacy. All the COVID-19 vaccines had a statistically significant reduction of risk for contracting symptomatic SARS-CoV-2 in comparison to the placebo, however, the maximum protection (RR 0.05) was with BNT126b2. The indirect comparison also revealed BNT126b2 vaccine confers the highest protection against symptomatic SARS-CoV-2 infection in comparison to all others included, with a 'P' score of 0.9771 followed by mRNA-1273, rAD26 & rAD5 and NVX-CoV2373. The evidence generated from this network meta-analysis indicates the good efficacy of all the included vaccines in preventing symptomatic COVID-19 as compared to placebo. The BNT126b2 vaccine was found to provide the highest protection against symptomatic SARS-CoV-2 among all included followed by mRNA-1273, rAD26 & rAD5, NVX-CoV2373 and others. Cochrane's 'Risk of Bias tool (RoB2)' was used for quality assessment. Assessment of inconsistency was not possible as no study compared two or more vaccines directly. Overall risk of bias among included studies was of 'some concern'.

Choi 2022 published an article on cross-neutralisation of Omicron subvariants after heterologous NVX-CoV2373 boosters: Comparison between prior SARS-CoV-2-infected and infection-naive individuals. Although NVX-CoV2373 booster vaccination presented promising immunogenicity, its cross-reactive immunogenicity against Omicron subvariants of SARS-CoV-2 was not reported. From March to April of 2022, the authors prospectively recruited individuals scheduled to receive NVX-CoV2373, including those who had completed two-doses (n = 9, aged 19 – 49 years) or three-doses (n=41, aged ≥ 60 years) vaccination approximately five months ago (from the date of publishing), who previously received either homologous or heterologous vaccination with ChAdOx1, BNT162b2, or mRNA-1273. Antinuclear capsid protein (anti-N) antibodies were measured in these individuals to determine prior SARS-CoV-2 infection status using the SARS-CoV-2 IgG assay. Participants in the third-dose booster group completed two-dose primary series vaccination 5.5 months (median) ago (from the date of Publishing), while those in the fourth-dose booster group received the prior third dose 4.7 months (median) ago (from the date of publishing). The median age of individuals with the third and fourth dose were 27 (range, 19 – 68 years) and 65 (range, 60 – 70) years, respectively. Neutralising antibody (nAb) titers against Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 were assessed in age/sex matched, prior-infected (*n*=9) and uninfected individuals (*n*=9), before (T0) and three

weeks (T1) after the fourth dose of vaccination. These values were compared with the titers of infection-naive individuals who received the third dose (*n*=6). Among infection-naive individuals, although fold-change was smaller after the fourth dose, third (3.8 – 14.7-fold) and fourth doses (1.8 – 2.5-fold) boosted the nAbs against both wild-type and Omicron subvariants. However, only a marginal increase (1.0 – 1.4-fold) in nAb titers was observed in prior-infected individuals after the fourth dose. Prior infection was associated with significant cross-reactive immunity against Omicron BA.5. Therefore, booster vaccination would be more helpful in infection-naive individuals. Before booster vaccination, the nAb titers against BA.1 or BA.5 variants were lower compared to those against the wild-type strain by a factor of 4 to 22. The fold difference between wild-type strain and Omicron subvariants became smaller in infection-naive individuals after booster vaccination. Additionally, the antibody kinetics up to 3 months among individuals ≥ 60 years who received NVX-CoV2373 as fourth-dose booster (n = 41), stratified by prior SARS-CoV-2 infection were investigated. Eighteen (43.9%) participants tested positive for anti-N antibody at baseline screening, and one participant became positive-converted during the follow-up period. Anti-S antibody titers were higher in prior-infected individuals than in infection-naive ones. Fourth-dose vaccination did not increase the anti-S antibody titers in prior-infected individuals, demonstrating ceiling effect. In conclusion, both third- and fourth-dose heterologous NVX-CoV2373 boosters enhanced cross-reactive immunity against Omicron BA.1/BA.5 subvariants among infection-naive individuals. Although repeated vaccination at short intervals showed ceiling effect in prior-infected individuals, which was consistent with previous reports, prior SARS-CoV-2 infection may provide better cross protection against diverse Omicron subvariants.

Hielscher 2022 published an article on NVX-CoV2373-induced cellular and humoral immunity towards parental SARS-CoV-2 and Variants of Concerns (VOCs) compared to BNT162b2 and mRNA-1273-regimens. In this observational study, 66 individuals were recruited to compare immunogenicity and reactogenicity of NVX-CoV2373 with BNT162b2 or mRNA-1273. Vaccine-induced antibodies were analyzed using ELISA and neutralisation assays, specific CD4 and CD8 T-cells were characterized based on intracellular cytokine staining using flow-cytometry after antigen-specific stimulation with parental spike or VOCs. Two doses of NVX-CoV2373 strongly induced anti-spike IgG, although IgG-levels were lower than after vaccination with BNT162b2 or mRNA-1273 (p=0.006). Regardless of the vaccine and despite different IgG-levels, neutralising activity towards VOCs was highest for Delta, followed by BA.2 and BA.1. The protein-based vaccine failed to induce any spike-specific CD8 T-cells which were detectable in 3/22 (14%) individuals only. In contrast, spike-specific CD4 T-cells were induced in 18/22 (82%) individuals, although their levels were lower (p<0.001), had lower CTLA-4 expression (p<0.0001) and comprised less multifunctional cells co-expressing IFNγ, TNFα and IL-2 (p=0.0007). Unlike neutralising antibodies, NVX-CoV2373-induced CD4 T-cells equally recognized all tested VOCs from Alpha to Omicron. In individuals with a history of infection, one dose of NVX-CoV2373 had similar immunogenicity as two doses in non-infected individuals. The vaccine was overall well-tolerated. NVX-CoV2373 strongly induced spike-specific antibodies and CD4 T-cells, albeit at lower levels as mRNA-regimens. Cross-reactivity of CD4 T-cells towards the parental strain and all tested VOCs may hold promise to protect from severe disease.

Tavakol 2022 published an article, "Can we succeed in the fight against SARS-CoV-2 with its emerging new variants"? The COVID_19 virus infected the human host by attaching to the angiotensin converting enzyme-2 (ACE2) and CD147 receptors in some human cells, resulting in cytokine storm and death. The new variants of the virus that caused concern are Alpha, Beta, Gamma, Delta, and Epsilon, according to the WHO label. However, Pango lineages designated them as B.1.1.7, B.1.351, P.1, B.1.617.2, and B.1.429. Variants may be progressively formed in one chronic COVID-19 patient and transmitted to others. They show some differences in cellular and molecular mechanisms. Mutations in the receptor-binding domain (RBD) and N-terminal domain (NTD) lead to alterations in the host's physiological responses. They show significantly higher transmissibility rates and viral load while evading neutralising antibodies at different rates. These effects are through mutations, deletion, and conformational alterations in the virus, resulting in the enhanced affinity of RBD to peptidase domain (PD) of ACE2 protein, peptidase domain (PD) virus entry, and spike conformational change. In the clinical laboratory, new variants may be diagnosed from other variants using specific primers for RBD or NTD. Some companies performed clinical trials on the efficacy of their vaccines on the new variants. Noticeably, Oxford/AstraZeneca showed 82% efficacy in the UK and failure against the Beta variant. Novavax's clinical trials showed the efficacy of 89.3 and 49.4% against the B.1.1.7 and Beta variants. The highest efficacy against the Beta variant among the mentioned vaccines belongs to Johnson & Johnson, with 57% efficacy for the Beta variant, while its efficacy against the Alpha variant is 72%. The studies on the vaccine's effectiveness in the Delta variant indicated that the first dose of both Pfizer and Oxford/AstraZeneca have 33% immunity in the patient, while the second dose exhibits the protection of 88% and 60% in vaccinated people, respectively. However, the Pfizer vaccine's neutralising antibody level for the Delta variant is five times less than the Wuhan variant. In other words, the Delta variant reduces the effectiveness of neutralising antibodies by Pfizer and Oxford/ AstraZeneca to 4.31- and 5.11-fold, respectively. The Beta variant's declined neutralisation efficacy was 6.29-fold. This difference may go back to the higher neutralising titter derived from two doses of Pfizer compared to two doses of Oxford/AstraZeneca. However, the hospitalization significantly decreased in Delta infected patients by Pfizer, Oxford/AstraZeneca, and Sinovac Biotech vaccines up to 96 and 92, and 90.3%, respectively. Declining the efficacy of neutralising antibodies has been shown in the Epsilon variant as well and happens through the remodeling of NTD, decreases the efficacy of neutralising antibodies. Therefore, vaccines should be designed against more than one epitope of the spike protein to overcome antibody escape derived from viruses' mutations. The nucleic acid deletion in virus proteins is a rapid evolution mechanism for antigenic drift. Although theoretical and experimental reports indicated the vaccine's low effectiveness against the new variants, it must be clinically investigated. The theory and experimental findings demonstrated that the position of N501Y is the site where neutralising antibodies act, while the 69/70 deletion will change the conformational shape of the RBD and immune responses. The decline response to the neutralising antibody with less affinity.

Codoni 2022 published an article on histological and serological features of acute liver injury after SARS-CoV-2 vaccination. Liver injury with autoimmune features after vaccination against Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) is increasingly reported. The authors investigated a large international cohort of patients with acute hepatitis arising after SARS-CoV-2 vaccination, focusing on histological and serological features. Patients without known pre-existing liver diseases and transaminase levels $\geq$ 5x the upper limit of normal within

3 months after any anti-SARS-CoV-2 vaccine and available liver biopsy were included. Fifty-nine patients were recruited; 35 females; median age 54 years; they were exposed to even different SARS-CoV-2 vaccines [mRNA based vaccines: mRNA-1273 (Moderna) and BNT162b2 (BioNTech/Pfizer); non-replicative virus vector vaccines: AZD1222 (AstraZeneca), Ad26.COV2.S (Johnson & Johnson) and Gam-COVID-Vac (Sputnik V); vaccine with inactivated SARS-CoV-2: BBIBP-CorV (Sinopharm); and protein based vaccines: NVX-CoV2373 (Novavax)] in various combinations before the diagnosis of liver injury. The hepatitis was diagnosed after the second vaccine dose in majority of patients. The median time from last vaccine dose to diagnosis of hepatitis was 24 days. Liver histology showed predominantly lobular hepatitis in 45 (76%) cases, predominantly portal hepatitis in 10 (17%), and other patterns in four (7%); seven had fibrosis Ishak stage ≥ 3, associated with more severe interface hepatitis. Autoimmune serology, centrally tested in 31 cases, showed anti-antinuclear antibody in 23 (74%), anti-smooth muscle antibody in 19 (61%), anti-gastric parietal cells in 8 (26%), anti-liver kidney microsomal in 4 (13%), anti-mitochondrial antibody in 4 (13%). Ninety-one percent were treated with steroids, ± azathioprine. Serum transaminase levels improved in all cases and were normal in 24/58 (41%) after three months, and in 30/46 (65%) after six months. Acute liver failure including hepatic encephalopathy manifested in a single patient, the only to require Liver Transplantation (LT) (113 days after re-exposure to BNT162b2 vaccine). Re-exposure to SARS-CoV-2 vaccines of 15 patients resulted in three relapses, however one subject who received BNT162b2 and NVX-CoV2373 did not relapse. Liver tests improved after three months in all patients. There were no significant differences between treated and untreated subjects in terms of demographics and clinical characteristics, vaccine type, time from vaccination to liver injury, histological and serological features, and outcome. In conclusion, acute liver injury with autoimmune features with temporal association with SARS-CoV-2 vaccination is likely to be a heterogeneous condition requiring a thorough work-up and careful follow-up. Patients are often treated with immunosuppression, with a good short-term response, though firm indications on when to start immunosuppression are needed, to avoid adverse effects. This study does not justify withholding SARS-CoV-2 vaccination, which has proven benefits by preventing severe COVID-19 disease and death of millions of people.

Salter 2022 published an article on Safety of Four COVID-19 Vaccines across Primary Doses 1, 2, 3 and Booster: A Prospective Cohort Study of Australian Community Pharmacy Vaccinations. Four COVID-19 vaccines are approved for use in Australia: Pfizer-BioNTech BNT162b2 (Comirnaty), AstraZeneca ChAdOx1 (Vaxzevria), Moderna mRNA-1273 (Spikevax) and Novavax NVX-CoV2373 (Nuvaxovid). It was sought to examine adverse events following immunisation (AEFI) at Days 3 and 42 after primary doses 1, 2, 3 and booster. An active vaccine safety surveillance was conducted from 130 community pharmacies in Australia integrated with AusVaxSafety, between August 2021 – April 2022. Main outcomes: AEFI at 0 – 3 days post-vaccination; medical review/advice at 3 days and 42 days post-vaccination; SARS-CoV-2 breakthrough infection by Day 42. Of 110,024 completed Day 3 surveys (43.6% response rate), 50,367 (45.8%) reported any AEFI (highest proportions: Pfizer 42%, primary dose 3; AstraZeneca 58.3%, primary dose 1; Moderna 65.4% and Novavax 58.8%, both primary dose 2). The most common AEFI reported across all doses/vaccines were local reactions, systemic aches and fatigue/tiredness. Overall, 2172/110,024 (2.0%) and 1182/55,329 (2.1%) respondents sought medical review on Days 3 and 42, respectively, and 931/42,318 (2.2%) reported breakthrough SARS-CoV-2 infection at Day 42. It was identified similar AEFI profiles but at lower

proportions than previously reported for Pfizer, AstraZeneca, Moderna and Novavax COVID-19 vaccines. Moderna vaccine was the most reactogenic and associated with higher AEFI proportions across primary doses 2, 3, and booster.

Upreti 2022 published an article on A Review on Immunological Responses to SARS-CoV-2 and Various COVID-19 Vaccine Regimens. The transmission of SARS-CoV-2 has caused serious health crises globally. So far, 7 vaccines that are already being assessed in Phase IV clinical trials are, Comirnaty/ Pfizer; Spikevax/Moderna (m RNA vaccine); Vaxzevria or Covishield; Ad26.COV2.S; Ad5-nCoV (adenoviral vector-based vaccine); CoronaVac and BBIBP-CorV (inactivated virus vaccine). Besides, there are about 280 vaccines that are undergoing preclinical and clinical trials including Sputnik-V, Covaxin or BBV152, and NVX-CoV2373. These vaccines are being studied for their immunological responses and efficiency against COVID-19 and have been reported to demonstrate effective T and B cell responses. However, the long-lasting immunity of these vaccine regimens still needs to be investigated. An in-depth understanding of the vaccine efficacy and immune control mechanism is imperative for the rational purposing and implementation of the vaccines. Hence, in this review, it was comprehensively discussed about the immune response induced in COVID-19 patients, as well as in the convalescent individuals to avoid reinfection. Moreover, it was also summarised the immunological responses and prophylactic efficacy of various COVID-19 vaccine regimens. This context has insights into the development of effective vaccines against SARS-CoV-2 and its variants in the future.

Twentyman 2022 published an article on Interim Recommendation of the Advisory Committee on Immunization Practices for Use of the Novavax COVID-19 Vaccine in Persons Aged ≥ 18 years - United States, July 2022. The NVX-CoV2373 (Novavax) COVID-19 vaccine is a recombinant spike (rS) protein nanoparticle vaccine with Matrix-M adjuvant to protect against infection with SARS-CoV-2, the virus that causes COVID-19. On July 13, 2022, the Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) for the Novavax vaccine for primary COVID-19 immunisation of unvaccinated adults aged ≥ 18 years, administered as 2 doses (5 µg rS and 50 µg Matrix-M adjuvant in each dose) 3 weeks apart (1). On July 19, 2022, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the Novavax vaccine in persons aged ≥ 18 years for the prevention of COVID-19. In the per-protocol efficacy analysis, vaccine efficacy (VE) against reverse transcription-polymerase chain reaction (RT-PCR)-confirmed symptomatic COVID-19 was 89.6% (95% CI = 82.4 – 93.8%). The Alpha variant (B.1.1.7) of SARS-CoV-2 was the predominant circulating variant during the period of case accrual for VE assessments. Cases of myocarditis or pericarditis were reported in temporal association with vaccination, suggesting a possible causal relationship. The ACIP recommendation for the use of the Novavax COVID-19 vaccine was interim and will be updated as additional information becomes available. The adjuvanted, protein subunit-based Novavax COVID-19 vaccine provides an additional option for unvaccinated adults, increasing flexibility for the public and for vaccine providers. Vaccination is important for protection against COVID-19.

Shrestha 2022 published an article on Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission. The first dominant SARS-CoV-2 Omicron variant BA.1 harbors 35 mutations in its Spike protein from the original SARS-CoV-2

variant that emerged late 2019. Soon after its discovery, BA.1 rapidly emerged to become the dominant variant worldwide and has since evolved into several variants. Omicron was of major public health concern owing to its high infectivity and antibody evasion. This article discussed the theories that have been proposed on the evolution of Omicron including zoonotic spillage, infection in immunocompromised individuals and cryptic spread in the community without being diagnosed. Added to the complexity of Omicron's evolution are the multiple reports of recombination events occurring between co-circulating variants of Omicron with Delta and other variants such as XE. Current literature suggests that the combination of the novel mutations in Omicron has resulted in the variant having higher infectivity than the original Wuhan-Hu-1 and Delta variant. However, severity was believed to be less owing to the reduced syncytia formation and lower multiplication in the human lung tissue. Perhaps most challenging was that several studies indicate that the efficacy of the available vaccines have been reduced against Omicron variant (8–127 times reduction) as compared to the Wuhan-Hu-1 variant. The administration of booster vaccine, however, compensates with the reduction and improves the efficacy by 12 – 35-fold. Concerningly though, the broadly neutralising monoclonal antibodies, including those approved by FDA for therapeutic use against previous SARS-CoV-2 variants, are mostly ineffective against Omicron except for Sotrovimab and recent reports suggest that the Omicron BA.2 was also resistant to Sotrovimab. Currently two new Omicron variants BA.4 and BA.5 are emerging and are reported to be more transmissible and resistant to immunity generated by previous variants including Omicron BA.1 and most monoclonal antibodies. As new variants of SARS-CoV-2 will likely continue to emerge it was important that the evolution, and biological consequences of new mutations, in existing variants be well understood.

Rydyznski Moderbacher 2022 published results of a Phase I/IIA trial in the Journal of Clinical Investigation characterised CD4+ and CD8+ humoral responses to NVX-CoV2373. Results demonstrated that participants had marked increases in spike-specific CD4+ and T follicular helper cells after both first and second dose of the vaccine. Vaccine-elicited CD4+ T cells were detectable within 7 days of primary immunisation and were comprised of both circulating T follicular helper (cTfh) cells and Th1 cells (IFN-γ+, TNF-α+, and IL-2+). The study also found that a subset of participants also mounted a spike-specific CD8+ T cell response, with vaccine-elicited CD8+ T cells demonstrating IFN-γ production. There was a direct correlation between spike-specific CD4+ T cells and the magnitude of SARS-CoV-2-neutralising antibody titers drawn later, indicative of robust cellular immune response capable of supporting humoral immune responses and recognising SARS-CoV-2 antigens.

Li 2022 published a systematic review and meta-analysis on efficacy, immunogenicity and safety of COVID-19 vaccines in patients ≥ 55 years in Frontiers in Immunology. A systematic literature review was conducted to identify randomized controlled trials on efficacy immunogenicity and safety of COVID-19 vaccines in adults ≥ 55 years. The authors identified 9 studies on efficacy in the population of interest, including 1 study on NVX-CoV2373. It was found that vaccines were efficacious against COVID-19 in older adults overall (79.49%, 95% CI: 60.55 – 89.34). NVX-CoV2373 was 1 of the 5 vaccines shown to be over 80% effective, at 88.9% efficacy (95% CI 12.8 – 98.6%). The authors identified 21 studies on immunogenicity of COVID-19 vaccines in adults ≥ 55 years, including 1 study on NVX-CoV2373. Overall, COVID-19 vaccines were shown to have high seroconversion rates (92.64%, 95% CI: 86.77 – 96.91) and geometric mean titer (GMT) of neutralising antibodies (standard mean difference SMD 3.56, 95% CI:

2.80 – 4.31). Estimated seroconversion for NVX-CoV2373 was 97.25% (95% CI 91.20 – 99.90). Vaccination was also found to provide a significant protection rate against severe disease (87.01%, 50.80 – 96.57). The vaccine type and number of doses were the primary influencing factors on efficacy and immunogenicity, with mRNA vaccines showing the best efficacy (90.72%, 95% CI: 86.82 – 93.46), highest seroconversion rate (98.52%, 95% CI: 93.45 – 99.98) and GMT (SMD 6.20, 95% CI: 2.02 – 10.39).

Oh 2022 published a systematic review and meta-analysis on comparative efficacy and safety of COVID-19 vaccines in the pre-delta variant era Vaccines (Basel). A systematic literature was conducted for Phase II and III randomized controlled trials (RCTs) assessing efficacy, immunogenicity and safety of COVID-19 vaccines up to 8-July-2021. The network meta-analysis used a Bayesian model and used the surface under the cumulative ranking to rank the comparisons between the vaccines. Fourteen studies assessing neutralising antibody response to live SARS-CoV-2 were identified, covering 11 vaccines and 10,208 participants. The levels of neutralising antibodies to live SARS-CoV-2 highly increased after the mRNA-1273 and NVX-CoV2373 vaccines. The mRNA platform vaccines showed higher efficacy and more adverse reactions than the other vaccines.

Review of published peer-reviewed scientific literature and available unpublished manuscripts did not identify any new and/or significant safety findings that would impact the overall benefit-risk balance of NVX-CoV2373.

12 OTHER PERIODIC REPORTS

Periodic reports (summary safety reports) submitted to relevant HA by SII (Covovax) and NVX (Nuvaxovid) are detailed in Table 14 below.

Table 14: Periodic SSRs submitted to HA

SSR No.	Reporting Interval	Data Lock Point
Nuvaxovid SSR No. 05	01-Jun-2022 to 30-Jun-2022	30-Jun-2022
Covovax SSR No. 10	01-Jun-2022 to 30-Jun-2022	30-Jun-2022
Nuvaxovid SSR No. 06	01-Jul-2022 to 31-Jul-2022	31-Jul-2022
Covovax SSR No. 11	01-Jul-2022 to 31-Jul-2022	31-Jul-2022
Nuvaxovid SSR No. 07	01-Aug-2022 to 31-Aug-2022	31-Aug-2022
Covovax SSR No. 12	01-Aug-2022 to 31-Aug-2022	31-Aug-2022
Nuvaxovid SSR No. 08	01-Sep-2022 to 30-Sep-2022	30-Sep-2022
Covovax SSR No. 13	01-Sep-2022 to 30-Sep-2022	30-Sep-2022
Nuvaxovid SSR No. 09	01-Oct-2022 to 31-Oct-2022	31-Oct-2022
Covovax SSR No. 14	01-Oct-2022 to 31-Oct-2022	31-Oct-2022
Nuvaxovid SSR No. 10 (Bimonthly)	01-Sep-2022 to 15-Nov-2022	15-Nov-2022
Nuvaxovid SSR No. 11	01-Nov-2022 to 30-Nov-2022	30-Nov-2022
Covovax SSR No. 15	01-Nov-2022 to 30-Nov-2022	30-Nov-2022

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 were obtained from controlled CTs.

14 LATE-BREAKING INFORMATION

No significant late breaking information with reference to Nuvaxovid 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

A tabulation of all signals new, ongoing and closed during the reporting interval are presented in Appendix 6 and Table 30.

During the reporting interval, new signals of diarrhoea, dyspnoea and tinnitus have been validated following assessment of PBRER V 1.0 procedure (EMEA/H/C/PSUSA/00010972/202206). Following the DLP, Signal Evaluation Reports (SER) were completed for diarrhoea, dyspnoea, and tinnitus. Complete evaluations are included in SERs in Appendix 19, Appendix 20 and Appendix 21.

Following the HA request received during the reporting interval, safety topics of Tachycardia with rhythm disorder abnormalities, Acute Coronary Syndrome associated with allergic reaction, Syncope and Menstrual disorders were evaluated. All three became validated signals and SERs along with addendum reports have been included in Appendix 22, Appendix 23, Appendix 24 and Appendix 25 respectively.

15.1.1 Anaphylaxis (Closed Signal)

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 Safety Review Team (SRT)'s decision and a request from EMA in the Pharmacovigilance Risk Assessment Committee (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 Adverse Event of Special Interest (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.

15.1.1.1 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-four ICSRs were retrieved for the interval (22 initial and 2 follow-up).

Cumulatively, 44 ICSRs were retrieved (38 females, 6 males; age range18 – 75 years when reported, median age 41.0 years). The 44 cumulative ICSRs included 44 AEs coded to PTs Anaphylactic reaction (n=30), Circulatory collapse (n=6), Anaphylactic shock (n=4),

Anaphylactoid reaction (n=2), Shock (n=1), and Type I hypersensitivity (n=1). All 44 cumulative AEs were designated serious, meeting IME criteria, of which 10 AEs additionally involved hospitalisation, 1 AE met other serious criteria, 1 AE involved patient disability, 1 AE was considered life-threatening, and 1 AE involved hospitalisation and was considered life-threatening.

Results of O/E with sensitivity analysis are presented in Table 16.

15.1.1.2 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 36).

Refer to Table 15 for stratification of AEs included in O/E analysis.

Table 15: Stratification of AEs Included in O/E Analysis

Total ICSRs	n=44
Total AEs	n=44
Number of AEs with TTO reported	38
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	6
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	40
Risk window 0 – 2 days	40
Risk window 0 – 7 days	41

Risk window 0 – 1 day: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within the risk window of 0 – 1 day (n=40), the observed rate showed an increase when compared to the expected rate with a statistically significant rate ratio (RR) of 16.65 (95% confidence interval [CI]: 11.89 – 22.67). When assessing by vaccinee dose number, there were increased and statistically significant O/E results for Dose 2 (n=4) with an RR of 8.61 (95% CI: 2.35 – 22.04) and for Booster doses (n=15) with an RR of 11.76 (95% CI: 6.59 – 19.40).

Risk window 0 – 2 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0 – 2 days (n=40), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 8.39 (95% CI: 6.00 – 11.43). When assessing by dose number, there were increased and statistically significant O/E results for Dose 2 (n=4) with an RR of 4.33 (95% CI: 1.18 – 11.09) and for Booster doses (n=15) with an RR of 5.93 (95% CI: 3.32 – 9.79).

Risk window 0 – 7 days: When accounting for all cumulative anaphylaxis 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 2.47 (95% CI: 1.77 – 3.35). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 16: 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	16.65 (11.89 – 22.67)	33.29 (23.79 – 45.34)	66.59 (47.58 – 90.68)
0 – 2 Days	8.39 (6.00 – 11.43)	16.79 (11.99 – 22.86)	33.57 (23.99 – 45.72)
0 – 7 Days	2.47 (1.77 – 3.35)	4.94 (3.54 – 6.70)	9.88 (7.09 – 13.40)
Dose 1			
0 – 1 Day	1.52 (0.05 – 8.47)	3.04 (0.09 – 16.95)	6.08 (0.18 – 33.89)
0 – 2 Days	0.76 (0.02 – 4.25)	1.53 (0.05 – 8.51)	3.06 (0.09 – 17.02)
0 – 7 Days	0.22 (< 0.01 – 1.22)	0.44 (0.01 – 2.44)	0.87 (0.03 – 4.87)
Dose 2			
0 – 1 Day	8.61 (2.35 – 22.04)	17.22 (4.69 – 44.07)	34.43 (9.38 – 88.14)
0 – 2 Days	4.33 (1.18 – 11.09)	8.66 (2.36 – 22.17)	17.32 (4.72 – 44.34)
0 – 7 Days	1.24 (0.34 – 3.16)	2.47 (0.67 – 6.33)	4.94 (1.35 – 12.66)
Booster			
0 – 1 Day	11.76 (6.59 – 19.40)	23.53 (13.18 – 38.81)	47.06 (26.35 – 77.61)
0 – 2 Days	5.93 (3.32 – 9.79)	11.87 (6.65 – 19.58)	23.74 (13.29 – 39.15)
0 – 7 Days	1.70 (0.95 – 2.81)	3.41 (1.91 – 5.62)	6.81 (3.82 – 11.24)

15.1.1.2.1 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 17 below. When accounting for all cumulative anaphylaxis reports meeting inclusion criteria (n=41) stratified by age and sex; the crude observed rate as reported in the total male group (n=5) showed a statistically significant increase when compared to the expected rate with an RR of 7.67 (95% CI: 2.48 – 17.90) and in the 40 – 49-year-old male group (n=2) with an RR of 14.29 (95% CI: 1.71 – 51.57). Non-statistically significant increases were observed in the 20 – 29-year-old male group (n=1), the 30 – 39-year-old male group (n=1), and the 50 – 59-year-old male group (n=1). The crude observed rate as reported in the total female group (n=36) showed an increase compared to the expected rate, and this increase was statistically significant with an RR of 18.37 (95% CI: 12.87 – 25.44). Results showed a statistically significant increase in the 20 – 29-year-old female group (n=3) with an RR of 13.62 (95% CI: 2.81 – 39.81), in the 30 – 39-year-old female group (n=11) with an RR of 25.08 (95% CI: 12.51 – 44.86), in the 40 – 49-year-old female group (n=11) with an RR of 21.64 (95% CI: 10.80 – 38.72), the 50 – 59-year-old female group (n=5) with an RR of 10.63 (95% CI: 3.45 – 24.82), and in the 60 – 69-year-old female group (n=4) with an RR of 19.25 (95% CI: 5.25 –

49.29). Non-statistically significant increase was observed in the 0 – 19-year-old female group (n=1).

Table 17: 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 – 86.10)	1	29.98 (0.90 – 166.98)
20 – 29	1	12.57 (0.38 – 70.04)	3	13.62 (2.81 – 39.81)
30 – 39	1	8.16 (0.24 – 45.46)	11	25.08 (12.51 – 44.86)
40 – 49	2	14.29 (1.71 – 51.57)	11	21.64 (10.80 – 38.72)
50 – 59	1	7.26 (0.22 – 40.42)	5	10.63 (3.45 – 24.82)
60 – 69	0	0 (0 – 44.05)	4	19.25 (5.25 – 49.29)
70 – 79	0	0 (0 – 95.82)	0	0 (0 – 56.32)
80+	0	0 (0 – 516.52)	0	0 (0 – 241.35)
Missing	0	N/A	1	N/A
Total	5	7.67 (2.48 – 17.90)	36	18.37 (12.87 – 25.44)

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

Demographic information on age was only available in exposure data from Australia, EU, Switzerland, Japan and New Zealand, and none reported the exposure data in the age categories requested. In addition, sex data are not available for any of the countries or region. 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 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.

15.1.1.4 Conclusion

A total of 44 AEs were reported cumulatively, most of which were coded to PT Anaphylactic reaction (n=30, 68.2%). The majority of the ICSRs involved females (n=38, 86.4%).

With the exclusion of 3 reports which fell outside of all risk windows, 41 AEs met inclusion criteria for the crude observed count for O/E analyses for the 0 – 7 days risk window. The 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.

The O/E result for all reports stratified by age and sex were not statistically significant except for the total male group, males 40 – 49 years, the total female group, and females 20 – 69 years.

This AESI underwent complete signal evaluation and was confirmed as signal. Anaphylaxis was added to RSI section of the IB and 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.

15.1.2 Myocarditis and Pericarditis (Closed Signal)

On 17-May-2022, the NVX Signal Management Committee (SMC) validated the signal of myocarditis and pericarditis based on a review of the increasing number of ICSRs being reported for myocarditis and pericarditis from the Australian TGA DAEN database and statistically significant results of O/E analyses which showed an increase in the observed reporting rate when compared to the expected rate.

On 24-May-2022, the US FDA requested that the pharmacovigilance plan (PVP) be updated to amend the risk of myocarditis and pericarditis from an "Important Potential Risk" to an "Important Identified Risk." Subsequently, on 27-May-2022, the European Medicines Agency in the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur Preliminary Assessment Report for the 3rd Monthly Safety Update requested that myocarditis and pericarditis be classified as signals in the fourth monthly Summary Safety Report (01-May-2022 to 31-May-2022).

A complete signal evaluation was performed based on which this signal was confirmed on 03-Aug-2022 and a SER was provided in PBRER V 1.0. Upon evaluation of the SER and additional data requested by EMA PRAC, as noted in the PRAC Assessment Report for SSR No.05, the signal of myocarditis and pericarditis was confirmed on 03-Aug-2022 and 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). The risk of myocarditis and pericarditis was renamed to myocarditis and/or pericarditis and was reclassified from an important potential risk to an important identified risk in the EU RMP V2.1 as of 01-Sep-2022. On 25-Oct-2022, the type II variation for updating the SmPC with myocarditis and/or pericarditis was approved by EMA.

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. The general methods for analysis as AESI are presented below.

15.1.2.1 Myocarditis

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

15.1.2.1.1 Results and Discussion

18 ICSRs were retrieved for the interval (11 initial and 7 follow-up).

Cumulatively, 21 ICSRs were retrieved (11 males, 9 females, 1 unspecified sex; age range 18 – 76 years, median age 32.0 years). The 21 cumulative ICSRs included 21 AEs coded to PTs Myocarditis (n=15) and Myopericarditis (n=6). All the 21 cumulative AEs were designated serious by convention, meeting IME criteria, with 7 AEs additionally involved hospitalisation.

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

15.1.2.1.2 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 36). TTO was reported for 12 out of the 21 AEs and was unknown for the remaining 9 AEs which were conservatively assessed as falling within the risk window. Of the 12 AEs with known TTO, it ranged from 0 – 4 days for 10 AEs. Amongst the other 2 AEs with known TTO, it was reported as 102 days for one AE which fell outside all risk windows and as 18 days for another AE which fell outside the risk windows of 0 – 7 and 0 – 14 days.

Therefore, after excluding the 2 AEs which fell outside the risk window of 0 – 7 and 0 – 14 days, 19 out of 21 AEs met TTO inclusion criteria for the observed count (n=19) for O/E analysis within these risk windows.

After excluding one AE with TTO of 102 days, 20 out of 21 AEs met TTO inclusion criteria for the observed count (n=20) for O/E analysis within the risk windows of 0 – 30 days and 0 – 42 days.

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

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

Total ICSRs	n=21
Total AEs	n=21
Number of AEs with TTO reported	12
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	9

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

AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 7 days	2
Risk window 0 – 14 days	2
Risk window 0 – 30 days	1
Risk window 0 – 42 days	1
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	19
Risk window 0 – 14 days	19
Risk window 0 – 30 days	20
Risk window 0 – 42 days	20

Risk window 0 – 7 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=19), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 20.85 (95% CI: 12.55 – 32.56). When assessing by dose number for the vaccinee, results were increased and statistically significant for Dose 2 (n=2) with an RR of 10.46 (95% CI: 1.26 – 37.76).

Risk window 0 – 14 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0 – 14 days (n=19), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 10.46 (95% CI: 6.30 – 16.33). 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 AEs meeting inclusion criteria within a risk window of 0 – 30 days (n=20), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 5.70 (95% CI: 3.49 – 8.81). 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=20), the observed rate showed an increase when compared to the expected rate, with a statistically significant RR of 4.40 (95% CI: 2.69 – 6.80). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 19: 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	20.85 (12.55 – 32.56)	41.70 (25.11 – 65.11)	83.39 (50.21 – 130.23)
0 – 14 Days	10.46 (6.30 – 16.33)	20.92 (12.59 – 32.66)	41.83 (25.19 – 65.32)
0 – 30 Days	5.70 (3.49 – 8.81)	11.41 (6.97 – 17.62)	22.82 (13.94 – 35.24)
0 – 42 Days	4.40 (2.69 – 6.80)	8.81 (5.38 – 13.61)	17.62 (10.77 – 27.21)
Dose 1			
0 – 7 Days	3.60 (0.11 – 20.08)	7.21 (0.22 – 40.16)	14.42 (0.43 – 80.31)
0 – 14 Days	1.81 (0.05 – 10.07)	3.62 (0.11 – 20.15)	7.23 (0.22 – 40.29)
0 – 30 Days	1.21 (0.04 – 6.74)	2.42 (0.07 – 13.48)	4.84 (0.15 – 26.96)
0 – 42 Days	1.21 (0.04 – 6.74)	2.42 (0.07 – 13.48)	4.84 (0.15 – 26.96)
Dose 2			
0 – 7 Days	10.46 (1.26 – 37.76)	20.92 (2.51 – 75.52)	41.84 (5.02 – 151.04)
0 – 14 Days	5.26 (0.63 – 18.98)	10.51 (1.26 – 37.95)	21.03 (2.52 – 75.91)
0 – 30 Days	2.48 (0.30 – 8.95)	4.96 (0.59 – 17.90)	9.91 (1.19 – 35.79)
0 – 42 Days	1.79 (0.21 – 6.45)	3.57 (0.43 – 12.89)	7.14 (0.86 – 25.78)
Booster			
0 – 7 Days	0 (0 – 8.32)	0 (0 – 16.64)	0 (0 – 33.27)
0 – 14 Days	0 (0 – 4.18)	0 (0 – 8.36)	0 (0 – 16.71)
0 – 30 Days	0 (0 – 1.97)	0 (0 – 3.94)	0 (0 – 7.88)
0 – 42 Days	0 (0 – 1.42)	0 (0 – 2.84)	0 (0 – 5.69)

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

When accounting for all cumulative myocarditis AESI reports (n=20), 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=10) showed a statistically significant increase in the observed rate compared to the expected rate with an RR of 4.63 (95% CI: 2.22 – 8.51). Results were increased and statistically significant in the total female group (n=9) with an RR of 4.38 (95% CI: 2.01 – 8.31). This was also the case for the 0 – 19-year-old male group (n=3) with an RR of 97.67 (95% CI: 20.19 – 285.53) and in the 20 – 29-year-old female group (n=3) with an RR of 16.85 (95% CI: 3.48 – 49.25). In the 20 – 29-year-old male group (n=2), 30 – 39-year-old male group (n=2), 40 – 49-year-old male group (n=2), 50 – 59-year-old male group (n=1), 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 20: 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	97.67 (20.19 – 285.53)	0	0 (0 – 329.82)
20 – 29	2	4.72 (0.57 – 17.05)	3	16.85 (3.48 – 49.25)
30 – 39	2	3.34 (0.40 – 12.06)	1	2.34 (0.07 – 13.05)
40 – 49	2	4.19 (0.50 – 15.14)	2	4.38 (0.53 – 15.83)
50 – 59	1	3.31 (0.10 – 18.46)	1	2.09 (0.06 – 11.64)
60 – 69	0	0 (0 – 20.22)	0	0 (0 – 11.70)
70 – 79	0	0 (0 – 33.47)	1	7.41 (0.22 – 41.26)
80+	0	0 (0 – 101.62)	0	0 (0 – 68.73)
Missing	0	N/A	1	N/A
Total	10	4.63 (2.22 – 8.51)	9	4.38 (2.01 – 8.31)

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

15.1.2.1.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2, 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.

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

Demographic information on age and sex was only available in exposure data from Australia and New Zealand, and neither country reported the exposure data in the age categories requested. 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. Differential spontaneous reporting rates by age and sex have been well documented following 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.

15.1.2.1.4 Conclusion

Cumulatively, there were 21 ICSRs identified myocarditis with a total of 21 AEs, the majority of which were coded to PT Myocarditis (n=15). More than half of the ICSRs involved males (n=11, 52.4%).

The O/E result showed an increased observed rate that was statistically significant. In addition, all risk windows present a statistically significant increase when considering all AEs.

The O/E result for all reports stratified by age and sex considering the 0 – 42 days risk window were not statistically significant except the results for total male group, the 0 – 19-year-old male group, the total female group, and the 20 – 29-year-old female group, all of which 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. Further details are provided in Section 15.1.2.3.

15.1.2.2 Pericarditis

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

15.1.2.2.1 Results and Discussion

During the reporting interval, 26 ICSRs were retrieved using the narrow search strategy (12 initial and 14 follow-up).

Cumulatively, 42 ICSRs were retrieved (21 males, 21 females; age range23-67 years when reported, median age 38.0 years). The 42 cumulative ICSRs included 42 AEs coded to PT Pericarditis (n=42). All 42 cumulative AEs were designated serious by convention, meeting IME criteria, of which 10 additionally met hospitalisation criteria, and one AE met hospitalisation and life-threatening criteria.

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

15.1.2.2.2 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 36 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 29 out of 42 AEs ranged from 0 – 15 days. The TTO was not reported in the other 13 AEs which were conservatively assessed as falling within the risk window.

After excluding 7 AEs with TTO ranging from 9 – 15 days, 35 out of 42 AEs met TTO inclusion criteria for the observed count (n=35) within the risk window of 0 – 7 days.

After excluding one AE with TTO of 15 days, 41 out of 42 AEs met TTO inclusion criteria for the observed count (n=41) within the risk window of 0 – 14 days.

All AEs met TTO inclusion criteria for the observed count (n=42) for O/E analysis within the risk window of 0 – 42 and 0 – 30 days.

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

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

Total ICSRs	n=42
Total AEs	n=42
Number of AEs with TTO reported	29
Number of AEs TTO missing (conservatively assessed as falling withing the risk window)	13
AEs with TTO falling outside risk windows (All AEs)	
Risk window 0 – 7 days	7
Risk window 0 – 14 days	1
Risk window 0 – 30 days	0
Risk window 0 – 42 days	0
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	35
Risk window 0 – 14 days	41
Risk window 0 – 30 days	42
Risk window 0 – 42 days	42

Risk window 0 – 7 days: When accounting for all cumulative pericarditis AEs meeting inclusion criteria within a risk window of 0 – 7 days (n=35), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 6.63 (95% CI: 4.62 – 9.23). 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=41), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 3.90 (95% CI: 2.80 – 5.29). When assessing by dose number, no O/E results both were 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=42), the observed rate, showed an increase when compared to the expected rate with a statistically significant RR of 2.04 (95% CI: 1.47 – 2.76). 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 pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=42), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 1.56 (95% CI: 1.12 – 2.11). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 22: 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	6.63 (4.62 – 9.23)	13.27 (9.24 – 18.45)	26.53 (18.48 – 36.90)
0 – 14 Days	3.90 (2.80 – 5.29)	7.79 (5.59 – 10.57)	15.58 (11.18 – 21.14)
0 – 30 Days	2.04 (1.47 – 2.76)	4.08 (2.94– 5.52)	8.16 (5.88 – 11.04)
0 – 42 Days	1.56 (1.12 – 2.11)	3.12 (2.25 – 4.22)	6.24 (4.50 – 8.44)
Dose 1			
0 – 7 Days	1.44 (0.17 – 5.20)	2.88 (0.35 – 10.41)	5.77 (0.69 – 20.82)
0 – 14 Days	0.72 (0.09 – 2.61)	1.45 (0.17 – 5.22)	2.89 (0.35 – 10.44)
0 – 30 Days	0.48 (0.06 – 1.74)	0.97 (0.12 – 3.49)	1.93 (0.23 – 6.98)
0 – 42 Days	0.48 (0.06 – 1.74)	0.97 (0.12 – 3.49)	1.93 (0.23 – 6.98)
Dose 2			
0 – 7 Days	0 (0 – 3.75)	0 (0 – 7.49)	0 (0 – 14.98)
0 – 14 Days	0 (0 – 1.88)	0 (0 – 3.76)	0 (0 – 7.53)
0 – 30 Days	0 (0 – 0.89)	0 (0 – 1.78)	0 (0 – 3.55)
0 – 42 Days	0 (0 – 0.64)	0 (0 – 1.28)	0 (0 – 2.56)
Booster			
0 – 7 Days	1.03 (0.21 – 3.01)	2.06 (0.43 – 6.03)	4.12 (0.85 – 12.06)
0 – 14 Days	0.69 (0.19 – 1.77)	1.38 (0.38 – 3.53)	2.76 (0.75 – 7.07)
0 – 30 Days	0.33 (0.09 – 0.83)	0.65 (0.18 – 1.67)	1.30 (0.36 – 3.34)
0 – 42 Days	0.24 (0.06 – 0.60)	0.47 (0.13 – 1.20)	0.94 (0.26 – 2.41)

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

When accounting for all cumulative Pericarditis AESI reports (n=42), stratified by age and sex, the crude observed rate as reported in the total male group (n=21) showed an increase when compared to the expected rate and this was statistically significant with an RR of 1.81 (95% CI: 1.12 – 2.77). Statistically significant increased results were observed in the 20 – 39-year-old

male group (n=13) with an RR of 3.41 (95% CI: 1.82 – 5.84). In the 40 – 59-year-old male group (n=7), results were increased, but this increase was not statistically significant. The crude observed rate as reported in the total female group (n=21) showed an increase when compared to the expected rate and this was statistically significant with an RR of 1.74 (95% CI: 1.08 – 2.67). Statistically significant increased results were observed in the 20 – 39-year-old female group (n=10) with an RR of 3.28 (95% CI: 1.57 – 6.03). In the 40 – 59-year-old female group (n=8), and the 60-year-old and older female group (n=3), 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 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 – 65.45)	0	0 (0 – 56.23)
20 – 39	13	3.41 (1.82 – 5.84)	10	3.28 (1.57 – 6.03)
40 – 59	7	1.43 (0.57 – 2.94)	8	1.68 (0.73 – 3.31)
60+	0	0 (0 – 1.76)	3	1.17 (0.24 – 3.41)
Missing	1	N/A	0	N/A
Total	21	1.81 (1.12 – 2.77)	21	1.74 (1.08 – 2.67)

15.1.2.2.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2, the possibility of overestimation of the observed count for myocarditis must be considered, as 13 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator falsely.

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

Demographic information on age and sex was only available in exposure data from Australia and New Zealand, and neither country reported the exposure data in the age categories requested. 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. Differential spontaneous reporting rates by age and sex have been well documented following 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.

15.1.2.2.4 Conclusion

Cumulatively, there were 42 ICSRs identified pericarditis with 42 AEs, all of which were coded to PT Pericarditis (n=42). Half of the ICSRs involved males (n=21, 50.0%).

The O/E result showed an increased observed rate that was statistically significant. In addition, all risk windows presented a statistically significant increase when considering all AEs.

The results of the O/E stratified by age and sex considering all reports and the 0 – 42 days risk window were not statistically significant, except for the total male group, the 20 – 39-year-old male group, the total female group, and the 20 – 39-year-old female group, all of which showed a statistically significant increase in the observed rate compared to the expected rate.

The AESI of myocarditis pooled with pericarditis has been identified as a confirmed signal. Further details are provided in Section 15.1.2.3.

15.1.2.3 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).

15.1.2.3.1 Results and Discussion

During the reporting interval, 44 ICSRs were retrieved using the prespecified search strategy for myocarditis and pericarditis (23 initial, 21 follow-up).

Cumulatively, 65 ICSRs were retrieved (32 females, 32 males, one individual of unspecified sex; age range 26 – 54 years, median age 37.0 years). The 65 cumulative ICSRs included 65 AEs coded to PTs Pericarditis (n=42), Myocarditis (n=15), Myopericarditis (n=6), and Carditis (n=2). All 65 cumulative AEs were designated as serious by convention, meeting IME criteria, of which 17 AEs additionally met hospitalisation criteria, and one AE met both hospitalisation and life-threatening criteria.

Results of O/E with sensitivity analyses and O/E analysis stratified by age and sex are presented below.

15.1.2.3.2 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 36 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".

The TTO was reported for 42 out of the 65 AEs and was unknown for the remaining 23 AEs which were conservatively assessed as falling within the risk window. The TTO ranged from 0 – 18 days in 42 out of 43 AEs with known TTO. In the other AE with known TTO, it was reported as 102 days, which fell outside all risk windows.

After excluding the AE with TTO of 102 days and additionally excluding 8 AEs with TTO ranging from 9 – 18 days, 56 of 65 AEs met TTO inclusion criteria for the observed count (n=56) within the risk window of 0 – 7 days.

After excluding the AE with TTO of 102 days and additionally excluding 3 AEs with TTO ranging from 15 – 18 days, 62 of 65 AEs met TTO inclusion criteria for the observed count (n=62) within the risk window of 0 – 14 days.

After excluding one AE with TTO of 102 days, 64 of 65 AEs met TTO inclusion criteria for the observed count (n=64) within the risk window of 0 – 30 days.

After excluding the AE with TTO of 102 days, 64 of 65 AEs met TTO inclusion criteria for the observed count (n=64) for O/E analysis within risk window 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 Myocarditis and Pericarditis

Total ICSRs	n=65
Total AEs	n=65
Number of AEs with TTO reported	42
Number of AEs TTO missing (conservatively assessed as falling within the risk window)	23
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	1
Total AEs included in O/E analysis (all AEs) stratified by risk window	
Risk window 0 – 7 days	56
Risk window 0 – 14 days	62
Risk window 0 – 30 days	64
Risk window 0 – 42 days	64

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=56), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 8.74 (95% CI: 6.60 – 11.35). 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=62), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 4.85 (95% CI: 3.72 – 6.22). 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=64), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 2.57 (95% CI: 1.98 – 3.29). 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 and pericarditis AEs meeting inclusion criteria within a risk window of 0 – 42 days (n=64), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 1.97 (95% CI: 1.52 – 2.52). When assessing by dose number, no O/E results were both increased and statistically significant.

Table 25: 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	8.74 (6.60 – 11.35)	17.48 (13.20 – 22.69)	34.95 (26.40 – 45.39)
0 – 14 Days	4.85 (3.72 – 6.22)	9.71 (7.44 – 12.44)	19.41 (14.88 – 24.88)
0 – 30 Days	2.57 (1.98 – 3.29)	5.15 (3.96 – 6.57)	10.29 (7.93 – 13.14)
0 – 42 Days	1.97 (1.52 – 2.52)	3.95 (3.04 – 5.04)	7.89 (6.08 – 10.08)
Dose 1			
0 – 7 Days	1.70 (0.35 – 4.97)	3.40 (0.70 – 9.93)	6.80 (1.40 – 19.87)
0 – 14 Days	0.85 (0.18 – 2.49)	1.71 (0.35 – 4.99)	3.41 (0.70 – 9.97)
0 – 30 Days	0.57 (0.12 – 1.67)	1.14 (0.24 – 3.34)	2.28 (0.47 – 6.67)
0 – 42 Days	0.57 (0.12 – 1.67)	1.14 (0.24 – 3.34)	2.28 (0.47 – 6.67)
Dose 2			
0 – 7 Days	1.60 (0.19 – 5.78)	3.20 (0.38 – 11.56)	6.40 (0.77 – 23.12)
0 – 14 Days	0.80 (0.10 – 2.90)	1.61 (0.19 – 5.81)	3.22 (0.39 – 11.62)
0 – 30 Days	0.38 (0.05 – 1.37)	0.76 (0.09 – 2.74)	1.52 (0.18 – 5.49)
0 – 42 Days	0.27 (0.03 – 0.99)	0.55 (0.07 – 1.98)	1.10 (0.13 – 3.96)
Booster			
0 – 7 Days	0.88 (0.18 – 2.58)	1.76 (0.36 – 5.16)	3.53 (0.73 – 10.32)
0 – 14 Days	0.59 (0.16 – 1.51)	1.18 (0.32 – 3.03)	2.36 (0.64 – 6.05)
0 – 30 Days	0.28 (0.08 – 0.71)	0.56 (0.15 – 1.43)	1.12 (0.30 – 2.85)
0 – 42 Days	0.20 (0.05 – 0.52)	0.40 (0.11 – 1.03)	0.80 (0.22 – 2.06)

15.1.2.3.2.1 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=64), stratified by age and sex, the crude as reported observed rate in the total male group (n=31), was increased compared with the expected rate, and this increase was statistically significant with an RR of 3.26 (95% CI: 2.22 – 4.63). Statistically significant increased results were also observed in the 0 – 19-year-old male group (n=3) with an RR of 28.71 (95% CI: 5.93 – 83.93), in the 20 – 29-year-old male group (n=11) with an RR of 7.54 (95% CI: 3.76 – 13.49), and in the 40 – 49-year-old male group (n=7) with an RR of 3.73 (95% CI: 1.50 – 7.69). The crude as reported observed rate in total female group (n=32), was increased when compared with the expected rate, and this increase was statistically significant with and RR of 3.21 (95% CI: 2.19 – 4.53). Statistically significant increased results were observed in the 20 – 29-year-old female group (n=8) with an RR of 10.85 (95% CI: 4.68 – 21.38), in the 30 – 39-year-old female group (n=7) with an RR of 4.23 (95% CI: 1.70 – 8.71), and in the 40 – 49-year-old female group (n=9) with an RR of 4.13 (95% CI: 1.89 – 7.85). 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=6), the 50 – 59-year-old male group (n=3), 50-59-year-old female group (n=3), 60 – 69-year-old female group (n=3) and in the 70 – 79-year-old female group (n=1).

Table 26: 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	28.71 (5.93 – 83.93)	0	0 (0 – 110.90)
20 – 29	11	7.54 (3.76 – 13.49)	8	10.85 (4.68 – 21.38)
30 – 39	6	2.64 (0.97 – 5.75)	7	4.23 (1.70 – 8.71)
40 – 49	7	3.73 (1.50 – 7.69)	9	4.13 (1.89 – 7.85)
50 – 59	3	1.65 (0.34 – 4.82)	3	1.08 (0.22 – 3.15)
60 – 69	0	0 (0 – 3.40)	3	1.88 (0.39 – 5.51)
70 – 79	0	0 (0 – 5.38)	1	1.32 (0.04 – 7.35)
80+	0	0 (0 – 17.98)	0	0 (0 – 15.17)
Missing	1	N/A	1	N/A
Total	31	3.26 (2.22 – 4.63)	32	3.21 (2.19 – 4.53)

15.1.2.3.3 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in 15.2, the possibility of overestimation of the observed count for myocarditis must be considered, as 23 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator falsely.

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

Demographic information on age and sex was only available in exposure data from Australia and New Zealand, and none of the countries reported the exposure data in the age categories requested. 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. Differential spontaneous reporting rates by age and sex have been well documented following 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.

15.1.2.3.4 Conclusion

Cumulatively, there were 65 ICSRs identified for the AESI of myocarditis and pericarditis with a total of 65 AEs. The most frequently reported PTs were Pericarditis (n=42), Myocarditis (n=15). Male to female ratio amongst the 64 reports were equal.

The O/E result for cumulative myocarditis and pericarditis showed an increased observed rate that was statistically significant.

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 40 – 49-year-old male group, the total female group, and the 20 – 49-year-old group.

The AESI of myocarditis and pericarditis was confirmed after complete signal evaluation. Core RMP was updated to classify myocarditis and/or pericarditis to an important identified risk. During the reporting interval, myocarditis and/or pericarditis was added to EU SmPC via Type 2 safety variation. Myocarditis and Pericarditis was added to the RSI section of the Investigator Brochure (IB). CCDS was updated to include Myocarditis and Pericarditis in Section 4.4 (Special Warnings and Precautions for use) and Section 4.8 (Undesirable effects). Myocarditis and pericarditis will be monitored to further characterise the risk via routine pharmacovigilance activities.

15.1.3 Paraesthesia (Closed Signal)

A signal of paraesthesia/hypoaesthesia was validated on 27-May-2022 pursuant to the EMA PRAC Assessment Report for the third monthly summary safety report (01-Apr-2022 to 30-Apr-2022) and a request from the TGA on 01-Jun-2022 to add paraesthesia/hypoaesthesia to the reference safety information in Australian NVX-CoV2373 Label. The request was to update the Product Information section 4.8 (Undesirable Effects) to include paraesthesia. A complete signal evaluation was performed, and the SER was presented in PBRER V 1.0. The signal of paraesthesia /hypoaesthesia was designated as confirmed and classified as a new identified risk, based on which, the TGA request to update local Australian Product Information Section 4.8

(Adverse Effects) was fulfilled. Additionally, the CCDS was updated to include paraesthesia/hypoaesthesia in Section 4.8 (Undesirable effects).

15.1.3.1 Results and discussion

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

During the reporting interval, 118 ICSRs were retrieved (106 initial and 12 follow-up).

Cumulatively, 358 ICSRs were retrieved (93 males, 264 females, 1 unknown sex, age range 13 – 81 years when reported). The 358 cumulative ICSRs included 444 AEs coded to PTs Paresthesia (n=278), Hypoaesthesia (n=119), Burning sensation (n=30), Hyperaesthesia (n=9), Dysaesthesia (n=6) and Hemiparaesthesia (n=2). Of the 444 AEs, 57 AEs were designated serious: 31 AEs met IME criteria, 3 AEs met other serious criteria, 4 AEs met disability criteria and 19 AEs involved hospitalisation.

15.1.3.2 Conclusion

Cumulatively, there were 358 ICSRs identified paresthesia with a total of 444 AEs, all of which were coded to PTs Paresthesia (n=278), Hypoaesthesia (n=119), Burning sensation (n=30), Hyperaesthesia (n=9), Dysaesthesia (n=6) and Hemiparaesthesia (n=2). Majority of the ICSRs involved females (n=264, 74 %).

This safety topic paraesthesia /hypoaesthesia underwent complete signal evaluation and was designated as confirmed. A safety variation was approved on 06-Sep-2022. The safety topic of paresthesia will continue to be monitored per routine pharmacovigilance activities.

15.1.4 Encephalitis and Encephalomyelitis (Closed Signal)

Pursuant to South Korean Health Authority communication, encephalitis and encephalomyelitis became a validated signal on 16-Jun-2022 and underwent signal evaluation based on broad search strategy (MedDRA HLT of Encephalitis non-viral infectious; Encephalitis of viral origin, Encephalitis NEC, and MedDRA SMQ (broad) of non-infectious encephalitis). The signal was refuted, and the SER was provided in PBRER V1.0 and SSR No.06.

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

15.1.4.1 Results and discussion

Three initial ICSRs were retrieved for the interval.

Cumulatively, 4 ICSRs were retrieved (3 females, 1 male; age range 42 – 67 years, median age 57.0 years). The 4 ICSRs included 4 AEs coded to PTs Noninfective encephalitis (n=2), Encephalitis (n=1), and Encephalitis post immunisation (n=1). All 4 cumulative AEs were

designated serious by convention, meeting IME criteria, with 2 of the AEs additionally involving hospitalisation.

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

15.1.4.2 Results of the O/E Analysis

TTO for two of 4 AEs were reported as 1 day and 28 days, both of which fell within the risk window of 0 – 42 days (refer to Table 36). The TTO was not reported for the two other AEs, and it was conservatively included in the O/E analyses. Therefore, all AEs met the inclusion criteria for the observed count (n=4). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.1.4.3 Conclusions

A total of 4 AEs were reported cumulatively, of which, 2 AEs were coded to Noninfective encephalitis (50%). The majority of ICSRs involved females (n=3, 75.0%)

The 4 ICSRs were assessed as Level 4 BC criteria for encephalitis due to insufficient clinical information. All ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates. No safety signal was identified.

15.1.5 Chest Pain and Chest Discomfort (Closed signal)

A signal of chest pain was validated on 15-Jun-2022, pursuant to a request from Health Canada in their assessment of 3rd monthly SSR (01-Apr-2022 to 30-Apr-2022). In addition, chest pain and chest discomfort were identified as a signal during electronic Reaction Monitoring Report (eRMR) review during the PBRER V 1.0 review period. A complete signal evaluation was performed, and the review did not suggest any apparent patterns or trends that would identify specific diagnoses beyond the chest pain/discomfort that may potentially relate to listed events or other topics under review (hypersensitivity, vaccination anxiety-related events and myocarditis/pericarditis) or would not be anticipated in the general population, hence this signal was refuted.

15.1.6 Dizziness (Closed Signal)

A signal of dizziness was validated on 15-Jun-2022, pursuant to a request from Health Canada in their assessment of 3rd monthly safety update report (01-Apr-2022 to 30-Apr-2022). A complete signal evaluation was performed and did not reveal any trends or patterns suggesting a safety signal. In most cases, the constellation of co-reported symptoms may be associated with reactogenicity or anxiety and did not suggest a specific neurologic pattern, hence this signal was refuted.

15.1.7 Tachycardia and Other rhythm abnormalities (Closed Signal)

A signal of tachycardia and other rhythm abnormalities was validated on 27-Jun-2022, pursuant to a request from PRAC in their PRAC assessment report for the 4th monthly safety update

(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. The SER and addendum (additional clinical trial data) are presented in Appendix 22.

15.1.8 Menstrual Disorders (Closed Signal)

A signal of menstrual disorders was validated on 27-Jun-2022, pursuant to a request from EMA PRAC, in their PRAC 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. The SER and addendum (additional clinical trial data) are presented in Appendix 25.

15.1.8.1 Results and Discussion

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

During the reporting interval, 40 initial ICSRs were retrieved.

Cumulatively, 106 ICSRs were retrieved (106 females, age range 20 – 53 years when reported). The 106 cumulative ICSRs included 168 AEs coded to PTs: Menstrual disorder (n=47), Heavy menstrual bleeding (n=37), Dysmenorrhoea (n=16), Amenorrhoea (n=15), Menstruation irregular (n=14); Intermenstrual bleeding (n=12), Polymenorrhoea (n=9); Menstruation delayed (n=6); Oligomenorrhoea (n=5); Hypomenorrhoea (n=4); Menstrual discomfort (n=2); and Premenstrual pain (n=1). Of the 168 AEs, 8 AEs were designated serious; six AEs met IME criteria and two AEs involved hospitalisation.

15.1.8.2 Conclusion

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, the signal of menstrual disorders was refuted.

15.1.9 Acute Coronary Syndrome Associated with Allergic Reaction (Closed signal)

A signal of Acute Coronary Syndrome (ACS) associated with hypersensitivity was validated on 29-Jul-2022, pursuant to a request from the pharmaceutical and Medical Device Agency (PMDA) in their assessment of the fifth monthly safety update (01-Jun-2022 to 30-Jun-2022). A complete signal evaluation was performed based on which it was noted that the overall findings did not suggest any apparent patterns or trend that would indicate a causal association between

acute coronary syndrome with allergic reactions and administration of Nuvaxovid. The signal was refuted. The SER is presented in Appendix 23.

15.1.10 Syncope (Closed signal)

On 25-Jul-2022, a signal of Syncope was validated, pursuant to PRAC's request in their assessment of the fifth monthly safety update (01-Jun-2022 to 30-Jun-2022). A complete signal evaluation was performed, and the SER is presented in Appendix 24 . Based on the signal evaluation. it was concluded that no additional signals or other etiologies beyond events associated with vaccine administration and related anxiety reactogenic reactions were identified beyond what is already listed in the SmPC in section 4.4 of Special Warnings and Precautions for Use. The signal was refuted.

15.1.11 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 after the DLP. The SER is presented in Appendix 19.

15.1.11.1 Results and Discussion

The clinical trial data was reviewed for unsolicited AEs using the PT: Diarrhoea. The search included unblinded data from Studies 2019nCoV-301, 2019nCoV-302 and 2019 CoV-501. The clinical trial data was balanced across active treatment and placebo arms with respect to the adverse event of diarrhea.

For the post-authorisation data, the global vaccine safety database was queried for cumulative ICSRs using the prespecified search strategy which included MedDRA PT of Diarrhoea, with a DLP of 16-Nov-2022. A total of 93 ICSRs were identified with the PT of diarrhea. The majority (84%) of these ICSRs were non-serious and contained co-reported PTs that are considered reactogenic or that may also indicate an alternative etiology. No specific etiology or pattern was noted.

Overall, no safety concerns have been observed during the cumulative review of the ICSRs with PT of diarrhoea. Analysis of ICSRs did not reveal any trends or patterns suggesting a safety signal or occurrence of diarrhea beyond that which is expected in the general population.

15.1.11.2 Conclusion

In conclusion, a causal association between NUVAXOVID™ and diarrhoea is not supported based on comprehensive review from clinical trials and post-authorisation data. The signal of diarrhoea is refuted.

15.1.12 Dyspnoea

A signal of dyspnoea was validated on 14-Nov-2022, pursuant to PRAC request in their assessment of PBRER V 1.0 (20-Dec-2021 to 19-Jun-2022). A complete signal evaluation was performed after the DLP. The SER is presented in Appendix 20.

15.1.12.1 Results and Discussion

The clinical trial database was reviewed for unsolicited AEs using the PT: Dyspnoea. The search included unblinded data from Studies 2019nCoV-301, 2019nCoV-302 and 2019 CoV-501. No treatment group difference was noted.

The post-authorisation safety database was searched for PTs: Dyspnoea, Dyspnoea exertional, with a DLP of 30-Nov-2022. A demographic summary of the retrieved ICSRs and event characteristics with case series of ICSRs with a seriousness criteria of hospitalisation or death are presented in Appendix 20. Dyspnoea is not considered a labeled event, it is included in the current version of the NUVAXOVID CCDS as a symptom of myocarditis or pericarditis. No safety concerns or trends were identified during this cumulative review. Clinical trial events were balanced across treatment and placebo groups. In most cases that were serious due to hospitalization, the constellation of co-reported symptoms may be associated with reactogenicity, or anxiety. Further, some serious events were described in association with anaphylaxis or hypersensitivity, for which shortness of breath or dyspnoea is a known symptom.

15.1.12.2 Conclusion

A causal association between NUVAXOVID and dyspnoea is not supported based on the current evidence. The signal of dyspnoea is refuted.

15.1.13 Tinnitus

A signal of "Tinnitus" was validated on 14-Nov-2022, pursuant to PRAC 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 Therapeutic Goods Administration, 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 after the DLP. The SER is presented in Appendix 21.

15.1.13.1 Results and Discussion

Tinnitus is not a labeled event as per current version of the CCDS. The clinical trial database was reviewed for unsolicited AEs using the PT: Tinnitus. The search included unblinded data from studies 2019nCoV-301, 2019nCoV-302, and 2019nCoV-501. In clinical trials, reporting rates of tinnitus were low, and no difference was reported between treatment arms following any dose. For the post-authorisation data, the global vaccine safety database was queried for cumulative ICSRs for PT of Tinnitus, with a DLP of 16-Nov-2022. A total of 67 cases of Tinnitus were

identified, with half of cases (50.75%) reported within 5 days following vaccination. Co-reported events consistent with local and/or systemic reactogenicity or anxiety-related reactions were noted in 71.64% of reports. Case-level (qualitative) analysis of serious post-marketing cases did not support a pattern or causal association due to presence of confounding factors or alternative explanations for the event. The characteristics and demographic summary of the retrieved ICSRs with case series of serious ICSRs are presented in Appendix 21.A disproportionality analysis of Eudravigilance Data Analysis System (EVDAS) eRMR (electronic Reaction Monitoring Report) report (1-Dec-2022 to 15-Dec-2022) revealed a Reporting Odds Ratio (ROR) of 3.35, with a changed status to "increased".

15.1.13.2 Conclusion

Tinnitus has been reported following vaccination with Nuvaxovid, in a pattern typically associated with stress or anxiety-related vaccination reactions. Based on current evidence, there is a reasonable causal association with the vaccine to confirm a safety signal. The signal of tinnitus was confirmed based on the post-marketing reports. The Safety Review Team (SRT) has endorsed the inclusion of tinnitus in the CCDS.

15.2 Other Safety Topics Not Considered as Signals

The following safety topics (not considered as signals) are being closely monitored based on recommendations for COVID-19 vaccines or upon request from HAs. All requests received from HAs cumulative through 19-Dec-2022 are listed on Adverse Events of Special Interest (AESI) and Observed to Expected Analysis.

Methods for AESI Analysis:

O/E analyses are performed for all AESI for which numerator data has been reported except for AESI related to pregnancy, since exposure is unknown in Women of Child-Bearing Age (WOCBA). 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). Although ICSRs reported by an identified healthcare professional either to the Health Authority or directly to NVX ("medically confirmed") were previously used as a stand-in for adjudication, further review indicated that these reports did not include diagnostic confirmation and therefore were not an appropriate surrogate for adjudication. 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.

Because of the imperfect data impacting O/E results of AESI, it is important to note that following the generation of statistically significant hypothesis generating O/E results, detailed

case series analyses are performed and TTOs are refined for descriptive analyses which include adjudication against case definitions, where available, and assessment of causal association with NUVAXOVID.

Sources of risk window, background incidence rate (IR), 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 HAs and social media sources. For countries with enhanced surveillance programs under emergency use authorisations:

- Where ICSRs are obtained by NVX from HA websites or databases, including TGA DAEN and European Medicines Agency's (EMA) EudraVigilance database, follow-up queries are not directly issued by NVX. Follow-up is solicited directly from TGA and downloaded from EVDAS for prioritised AESI cases to obtain information necessary for O/E calculations and case adjudication.
- Where ICSRs are not available to the sponsor, known exposure in that country is not included in O/E calculations for any purpose (calculation of expected counts or calculation of AESI reporting rates). For example, although accounting for over half of worldwide exposure, NUVAXOVID doses administered in South Korea are excluded from the denominator of O/E, which is expected to bias overall results. This exclusion is purposely done to reduce the possibility of immortal time-bias created by insufficient reporting of individual case reports from this country. Aggregate data from South Korea is summarised in Section 6.3.1.
- 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 distortion (underestimation) of the O/E results.

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:

- The limited sample size due to recent market authorisation of a new product may reduce the statistical power of these analyses, especially for sub analyses such as analyses per dose number or stratified analyses per age and sex.
- For the overall O/E results, AE reports with unknown TTO were conservatively included in observed counts and the possibility that the numerator was falsely 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 2021) study and the US FDA Biologics Effectiveness and Safety (Moll 2023) Initiative were preferred sources of background rate data (refer to Appendix 10).

In situations where background rates for certain AESI could not be identified in such sources, may be necessary to utilise scientific literature. Overall, the potential for differences between the data and methods used to generate the expected background rates means that the expected rates may not reflect the types of data from observed case data. Therefore, the potential for biased O/E results based on differences in observed versus expected rates cannot be fully excluded.

Overview of AESI Results

ICSRs with MedDRA PTs falling under the following AESI search strategies have been identified across cumulative and/or interval data:

- Anaphylaxis (refer to Section 15.1.1)
- Autoimmune Hepatitis (refer to Section 15.2.1)
- Autoimmune Thyroiditis (refer to Section 15.2.2)
- Bell's Palsy (refer to Section 15.2.3)
- Cerebral Venous Sinus Thrombosis (refer to Section 15.2.4)
- Chronic Fatigue Syndrome (refer to Section 15.2.5)
- Encephalitis, Encephalomyelitis (refer to Section 15.1.4)
- Fibromyalgia (refer to Section 15.2.6)
- Generalised Convulsions (refer to Section 15.2.7)
- Guillain-Barré Syndrome (refer to Section 15.2.8)
- Haemorrhagic Stroke (refer to Section 15.2.9)
- Ischaemic Stroke (refer to Section 15.2.10)
- Multiple Sclerosis (refer to Section 15.2.11)
- Myocardial Infarction (refer to Section 15.2.12)
- Myocarditis and Pericarditis (refer to Section 15.1.2)
- Optic Neuritis (refer to Section 15.2.13)
- Postural Orthostatic Tachycardia Syndrome (refer to Section 15.2.14)
- Rheumatoid Arthritis (refer to Section 15.2.15)
- Spontaneous Abortion (refer to Section 15.2.16)
- Thrombocytopenia (refer to Section 15.2.17)
- Venous Thromboembolism (refer to Section 15.2.18)

15.2.1 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)

15.2.1.1 Results and Discussion

A single initial ICSR was retrieved for the interval.

Cumulatively, one ICSR was retrieved (female, age 44 years). The single cumulative ICSR included one AE coded to PT Autoimmune hepatitis (n=1). This AE was designated as serious by convention, meeting IME criteria and involved hospitalisation.

Results of O/E analyses are presented below.

15.2.1.2 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 36). Hence, this single AE did not meet the inclusion criteria for the observed count for O/E analyses.

15.2.1.3 Conclusion

Due to insufficient information in the case, absence of temporal relationship, and confounding COVID-19, a causal association could not be established. This single ICSR did not meet the TTO inclusion criteria for O/E analyses.

No safety signal was identified.

15.2.2 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).

15.2.2.1 Results and Discussion

Two initial 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 Thyroiditis (n=1), Autoimmune Thyroiditis (n=1) and Basedow's disease (n=1). One of the AEs (thyroiditis) was non-serious, AE (Basedow's disease) was designated as serious by convention, meeting IME criteria and other AE (autoimmune thyroiditis) was serious due to disability and meeting IME criteria.

Results of O/E analyses are presented below.

15.2.2.2 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 36). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.2.3 Conclusion

There was insufficient information to establish a causal association. Three ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.3 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).

15.2.3.1 Results and Discussion

Five ICSRs were retrieved for the interval (4 initial and 1 follow-up).

Cumulatively, 11 ICSRs were retrieved (6 females, 4 males, 1 unknown sex; age range 30 – 62 years when reported, median age 49.5 years). The 11 cumulative ICSRs included documentation of 13 AEs coded to PTs corresponding to Bell's palsy. One of these AEs occurred before vaccination (TTO = -21 days) and was therefore excluded from analyses in this report. Thus, the 11 cumulative ICSRs included 12 AEs that were considered for analyses, coded to PTs Facial paralysis (n=7), Bell's palsy (n=4), and Facial paresis (n=1). All 12 AEs were designated serious: 11 AEs met IME criteria, with 1 of these AEs additionally meeting other serious criteria and one of these AEs additionally involving hospitalisation; one AE (PT: Facial paresis) in a female of unknown age met hospitalisation criteria only.

Results of O/E analyses are presented below.

15.2.3.2 Results of the O/E Analysis

The TTO for 8 of 12 AEs ranged from 0 – 3 days which are within the risk window of 0 – 42 days (refer to Table 36). TTOs were not reported for the other 4 AEs and were conservatively included in the O/E analyses. Therefore, all AEs met inclusion criteria for the observed count (n=12). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.3.3 Conclusion

Cumulatively, 12 AEs were reported, most of which were coded to PT Facial paralysis (n=7, 58.3%).

Although a temporal relationship was seen for most AEs, due to a lack of details regarding clinical presentation of Bell's palsy and limited medical history reported, there was insufficient information to establish a causal association. All ICSRs met TTO inclusion criteria and results of O/E and sensitivity analyses showed lower than expected rates.

No safety signal was identified.

15.2.4 Cerebral Venous Sinus Thrombosis

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

15.2.4.1 Results and Discussion

A single initial ICSR was retrieved for the interval.

Cumulatively, one ICSR was retrieved (unspecified sex and age). The single cumulative ICSR included one AE coded to PT: Cerebral venous sinus thrombosis. This AE was designated as serious by convention, meeting IME criteria. No details were provided in the report other than event terms, precluding meaningful analysis.

Results of O/E analyses are presented below.

15.2.4.2 Results of the O/E Analysis

The TTO for the single AE was not reported and conservatively was included in the O/E analyses. Therefore, the AE met inclusion criteria for the observed count (n=1). O/E and sensitivity analyses results showed that the observed rate was increased compared to the expected rate but this increase was not statistically significant.

15.2.4.3 Conclusion

Due to lack of clinical details, no relevant safety information was identified.

No safety signal was identified.

15.2.5 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).

15.2.5.1 Results and Discussion

Two ICSRs were retrieved for the interval (one initial and one follow-up).

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

Results of O/E analyses are presented below.

15.2.5.2 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 36). 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 50% sensitivity analyses results showed that the observed rate was lower than the expected rate. The 25% sensitivity analysis results showed that the observed rate was higher than expected, but not statistically significant.

15.2.5.3 Conclusion

No relevant safety information was identified in these reports to establish a definitive causal association. All ICSRs met TTO inclusion criteria for O/E analyses, which showed observed rates were lower than expected rates overall and at 50% sensitivity. The increase in observed rate compared to expected rate at 75% sensitivity was not statistically significant.

No safety signal was identified.

15.2.6 Fibromyalgia

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

15.2.6.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, one ICSR (male, unknown age) was retrieved. The single ICSR included one non-serious AE coded to PT Fibromyalgia. The reported verbatim was 'fibromyalgia worsened' occurring two days after receiving the first dose.

Results of O/E analyses are presented below.

15.2.6.2 Results of the O/E Analysis

The TTO was reported as 2 days for this single report which is within the risk window of 0 – 42 days (refer to Table 36). O/E and sensitivity analyses results showed the observed rate was lower than the expected rate.

15.2.6.3 Conclusion

No relevant safety information was identified in the report. The single ICSR met TTO inclusion criteria for O/E analyses, which showed observed rates were lower than expected rates. There was insufficient information to establish a causal association.

No safety signal was identified.

15.2.7 Generalised Convulsions

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

15.2.7.1 Results and Discussion

Seven ICSRs were retrieved for the interval (five initial and two follow-up).

Cumulatively, 10 ICSRs were retrieved (8 females, 2 males, age range 19 – 76 years when reported). The 10 cumulative ICSRs included 11 AEs coded to PTs Seizure (n=6), Clonic convulsion (n=1), Epilepsy (n=1), Febrile convulsion (n=1), Generalised tonic-clonic seizure (n=1), and Postictal state (n=1). Ten of 11 AEs were designated as serious by convention, meeting IME criteria, of which, 2 AEs additionally met hospitalisation criteria, 2 AEs met both hospitalisation and LT criteria, one AE met other seriousness criteria, and one AE had a fatal outcome.

Results of O/E analyses are presented below.

15.2.7.2 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 36). Two reports with TTO of 92 and 38 days are outside the risk windows and were excluded from O/E analysis. The TTO was known for the other 6 AEs which are within all the risk windows (range 0 – 6 days). The TTO was not reported for 2 AEs which conservatively were included in the O/E analyses. A total of 8 AEs met the inclusion criteria for the observed count (n=8) for O/E analyses.

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=7), the observed rate showed a non-statistically significant increase compared to the expected rate. However, when assuming 75% underreporting, there was a statistically significant increase in the observed rate versus the expected rate with an RR of 4.03 (95% CI: 1.62 – 8.31).

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=8) and 0 – 2 days (n=7) 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.

15.2.7.3 Conclusion

No relevant safety information was identified in reports to establish a causal association. Eight of the 10 cumulative reports met TTO inclusion criteria for O/E analyses, which showed that the

observed rate was lower than the expected rate when using risk windows of 0 – 2 and 0 – 7 days. O/E analysis calculated using risk window of 0 – 1 days showed that the observed rate was increased compared to the expected rate, but this increase was not statistically significant unless assuming 75% underreporting.

No safety signal was identified.

15.2.8 Guillain-Barré Syndrome

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

15.2.8.1 Results and Discussion

Three initial ICSRs were retrieved for the interval.

Cumulatively, 5 ICSRs were retrieved (1 female, 2 males, 2 unknown sex, age range 18 – 76 years when reported). The 5 cumulative ICSRs included 5 AEs coded to PT Guillain-Barré syndrome (n=5). The 5 cumulative AEs were designated serious by convention, meeting IME criteria, with one AE additionally involving hospitalisation.

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

15.2.8.2 Results of the O/E Analysis

The TTO of 3 of 5 AEs ranged from 3 – 12 days, which are within the risk window of 0 – 42 days (refer to Table 36). The TTO was not reported for the two other AEs which conservatively were included in the O/E analyses (n=5). The observed rate showed a non-statistically significant increase compared to the expected rate. However, when assuming 75% underreporting, there was a statistically significant increase in the observed rate compared to the expected rate, with RR of 5.55 (95% CI 1.80 – 12.96).

15.2.8.3 Conclusion

All five cumulative reports were assessed as Level 4 BC criteria for GBS due to insufficient clinical information. One of the 5 reports of GBS was confounded by pre-existing polyneuropathy secondary to past chemotherapy, inconclusive diagnostic testing, and lack of definitive clinical diagnosis. All ICSRs met TTO inclusion criteria for O/E analyses, which showed the observed rate was increased compared to the expected rate. However, this increase was not statistically significant as reported or when assuming 50% underreporting. Though the observed rate was significantly increased compared to the expected rate when assuming underreporting at 75%, this sensitivity analysis likely overestimates the rate of incomplete reporting in the current setting of the COVID-19 pandemic given increased public awareness and concerns about vaccine safety, more stringent reporting requirements for HCPs, and enhanced pharmacovigilance programs globally.

No safety signal was identified.

15.2.9 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).

15.2.9.1 Results and Discussion

10 ICSRs were retrieved for the interval (8 initial and 2 follow-up).

Cumulatively, 10 ICSRs were retrieved (5 males, 4 females, 1 individual of unspecified sex, age range 31 – 96 years when reported). The 10 cumulative ICSRs included 10 AEs coded to PT Cerebrovascular accident (n=10). All AEs were designated as serious by convention, meeting IME criteria of which 5 AEs additionally involved hospitalisation and 2 AEs had a fatal outcome.

Of note: The 10 ICSRs with AEs coded to PT Cerebrovascular accident (n=10) are the same ICSRs as noted in 15.2.10. As the type of cerebrovascular accident was not indicated, the ICSRs appeared in both the haemorrhagic stroke and ischaemic stroke search strategies.

15.2.9.2 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 36). TTO was not reported for the other 5 AEs and conservatively included in the O/E analysis. TTO for the remaining one AE was 31 days, hence fell outside the risk window. Therefore, excluding one AE falling outside the risk window, a total of 9 AEs met inclusion criteria for the observed count (n=9). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.9.3 Conclusion

Due to lack of pertinent clinical information and diagnostic work-up of haemorrhagic stroke, no definitive causal association could be established. Nine ICSRs met TTO inclusion criteria and results of O/E analyses showed a lower than expected rate.

No safety signal was identified.

15.2.10 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).

15.2.10.1 Results and Discussion

12 ICSRs were retrieved for the interval (10 initial and two follow-up).

Cumulatively, 14 ICSRs were retrieved (6 males, 6 females, 2 individuals of unspecified sex, age range 31 – 96 years when reported). The 14 cumulative ICSRs included 14 AEs coded to PTs Cerebrovascular accident (n=10), Brain stem infarction (n=1) Carotid artery disease (n=1),

Ischaemic stroke (n=1) and Transient ischaemic attack (n=1). All 14 AEs were designated as serious by convention, meeting IME criteria, of which 8 AEs additionally involved hospitalisation and 2 AEs had fatal outcome (PT: Cerebrovascular accident).

Note: The 10 ICSRs with AEs coded to PT Cerebrovascular accident (n=10) are the same ICSRs as noted in Section 15.2.9. As the type of cerebrovascular accident was not indicated, these ICSRs appeared in both the haemorrhagic stroke and ischaemic stroke search strategies.

Results of O/E analyses are presented below.

15.2.10.2 Results of the O/E Analysis

The TTO for 7 of 13 AEs ranged from 1 – 21 days which fell within the risk window of 0 – 28 days (refer to Table 36). TTO was not reported in 6 of the 13 AEs and these AEs were conservatively included in O/E analysis. TTO for the remaining one AE was 31 days, hence fell outside the risk window. Therefore, excluding one AE falling outside the risk window, 13 AEs met inclusion criteria for the observed count (n=13) for O/E analysis. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.10.3 Conclusion

Due to lack of pertinent clinical information and diagnostic work-up of ischaemic stroke, no definitive causal association could be established. Thirteen ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.11 Multiple Sclerosis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Multiple sclerosis acute and progressive (refer to Appendix 12).

15.2.11.1 Results and Discussion

A single follow-up ICSR was retrieved for the interval.

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

One serious report of multiple sclerosis relapse (coded to MedDRA PT Multiple sclerosis) which met criteria of disability, concerned a 63-year-old female and reportedly occurred within 1 day of vaccination. The reported symptoms included a feeling of vibration, loss of energy, restlessness, and sleep disorder. Medical history included multiple sclerosis since 1985, noted in addition as encephalitis disseminata, which had been pre-existing for years. At the time of reporting, the

event outcome was not recovered. The remaining 2 reports of multiple sclerosis relapse were for 1 male and 1 female, and no relevant safety information was identified in these reports.

Results of O/E analyses are presented below.

15.2.11.2 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 36). O/E and 50% sensitivity analyses results showed that the observed rate was lower than the expected rate. Results of 75% sensitivity analyses showed that the observed rate was higher than the expected rate but not statistically significant.

15.2.11.3 Conclusion

Overall, there was insufficient definitive evidence to establish a causal association. All ICSRs met the TTO inclusion criteria and results of O/E analyses showed a lower than expected rate. No safety signal was identified.

Overall, there was insufficient definitive evidence to establish a causal association.

No safety signal was identified.

15.2.12 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).

15.2.12.1 Results and Discussion

11 ICSRs were retrieved for the interval (9 initial and 2 follow-up).

Cumulatively, 16 ICSRs were retrieved (8 males, 5 females, 3 individuals of unspecified sex, age range 24 – 93 years when reported). The 16 cumulative ICSRs included 16 AEs coded to PTs Troponin increased (n=6), Acute myocardial infarction (n=2), Myocardial infarction (n=7), and Acute coronary syndrome (n=1). 13 out of 16 AEs were serious. Of these 13 AEs, 12 AEs were designated as serious by convention, meeting IME criteria, of which 4 AEs additionally involved hospitalisation. One AE coded to PT: Troponin increased was serious due to hospitalisation only and one AE coded to Myocardial infarction resulted in a fatal outcome.

Results of O/E analyses are presented below.

15.2.12.2 Results of the O/E Analysis

The TTO for 6 of 11 AEs ranged from 0 – 14 days which fell within the risk window of 0 – 28 days (refer to Table 36). Two AEs with TTO of 60 and 71 days respectively, fell outside the risk window, hence, was excluded from the O/E analysis. TTO was not reported in the other 8 AEs which were conservatively included in the O/E analyses. Therefore 14 out of 16 AEs met

TTO inclusion criteria for the observed count (n=14) for O/E analysis. O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.12.3 Conclusion

No relevant safety information was identified in these reports to establish a causal association. Fourteen out of 16 AEs met TTO inclusion criteria and results of O/E analyses showed lower than expected rate.

No safety signal was identified.

15.2.13 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).

15.2.13.1 Results and Discussion

A single follow-up ICSR was retrieved for the interval.

Cumulatively, 1 ICSR was retrieved. The single cumulative ICSR included one AE coded to PT Optic neuritis (n=1). This AE was designated as serious by convention, meeting IME criteria.

This report concerned a 37-year-old female who experienced blurred vision, pain during movement in the right eye, headache, eye inflammation on the right side, and muffled hearing 10 days after vaccination with co-reported events of lethargy, hyperhidrosis, and ear congestion. She was later diagnosed with idiopathic orbital inflammatory disease and retinal neuritis in the right eye. Medical history included attention deficit hyperactivity disorder and received concomitant medication of dexamphetamine.

Results of O/E analyses are presented below.

15.2.13.2 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 36). O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.13.3 Conclusion

A possible confounder in this report was the concomitant medication, there was no information on diagnostic tests. This ICSR met the TTO inclusion criteria and results of O/E analyses showed a lower than expected rates. No safety signal was identified.

A possible confounder in this report was the concomitant medication, there was no information on diagnostic tests. No safety signal was identified.

15.2.14 Postural Orthostatic Tachycardia Syndrome

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

15.2.14.1 Results and Discussion

Two ICSRs were retrieved for the interval (one initial and one follow-up).

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 POTS (n=2). Of the 2 AEs, one AE was designated as serious by convention, meeting IME criteria.

Results of O/E analyses are presented below.

15.2.14.2 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 36). 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.

15.2.14.3 Conclusion

No relevant safety information was identified in these reports to establish a causal association.

No safety signal was identified.

15.2.15 Rheumatoid Arthritis

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

15.2.15.1 Results and Discussion

Two follow-up ICSR were retrieved for the interval.

Cumulatively, 3 ICSRs were retrieved (2 females, 1 male, age range 29 – 46 years when reported). The 3 cumulative ICSRs included 3 AEs coded to PT: Rheumatoid arthritis (n=3). These 3 AEs were designated as serious by convention, meeting IME criteria.

Results of O/E analyses are presented below.

15.2.15.2 Results of the O/E Analysis

The TTO for 2 of 3 AEs was 0 and 3 days respectively which fell within the risk window of 0 – 42 days (refer to Table 36). The TTO was not reported for the other AE which was

conservatively included in O/E analyses. Therefore, all 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.

15.2.15.3 Conclusion

No relevant safety information was identified in these reports to establish a causal association.

No safety signal was identified.

15.2.16 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).

15.2.16.1 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 WOCBA.

15.2.16.2 Conclusion

Meaningful analysis was limited due to lack of information about gestational age at time of event, risk factors including medical and obstetrical history or time of vaccine with respect to last menstrual period. Hence the available information was not suggestive of a causal association between the event and vaccine.

No safety signal was identified.

15.2.17 Thrombocytopenia

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

15.2.17.1 Results and Discussion

Two follow-up ICSRs were retrieved for the interval.

Cumulatively, 5 ICSRs were retrieved (5 females, age range 23 – 63 years when reported). The 5 cumulative ICSRs included 6 AEs coded to PTs Thrombocytopenia (n=5) and Immune thrombocytopenia (n=1). All 6 AEs were designated as serious by convention, meeting IME

criteria, of which 2 AEs additionally involved hospitalisation, and one AE met other serious criteria.

Results of O/E analyses are presented below.

15.2.17.2 Results of the O/E Analysis

The TTO for three of six AEs ranged from 7 – 34 days which are within the risk window of 0 – 42 days (refer to Table 36). TTO was not reported in the other 2 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 two AEs into one case, five AEs met inclusion criteria for the observed count (n=5) for O/E analysis. The O/E and sensitivity analyses results showed that the observed rate was lower than the expected rate.

15.2.17.3 Conclusion

No relevant safety information was identified in these reports to establish a causal association. All ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.2.18 Venous Thromboembolism

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

15.2.18.1 Results and Discussion

12 ICSRs were retrieved for the interval (11 initial and 1 follow-up).

Cumulatively, 19 ICSRs were retrieved (6 males, 11 females, 2 individuals of unspecified sex, age range 29 - 85 years when reported). The 19 cumulative ICSRs included 22 AEs coded to PTs Pulmonary embolism (n=11), Deep vein thrombosis (n=3), Thrombophlebitis (n=3), Superficial vein thrombosis (n=2), Venous thrombosis (n=2), and Cerebral venous sinus thrombosis (n=1). Eighteen out of 22 AEs were serious. Of these 18 AEs, 16 AEs were designated as serious by convention, meeting IME criteria, of which 8 AEs additionally involved hospitalisation and 2 met hospitalisation and LT criteria. One AE coded to PT: Venous thrombosis was serious due to hospitalisation only and one AE coded to Superficial vein thrombosis met disability and LT criteria.

Results of O/E analyses are presented below.

15.2.18.2 Results of the O/E Analysis

The O/E analysis was performed for the risk window of 0 – 28 days (refer to Table 36). Of the 22 AEs, TTO was reported for 20 AEs and two AEs with missing TTO were conservatively assessed as falling within the risk window. The TTO for 18 out of 22 AEs with known TTO ranged from 1 – 28 days and the TTO for the other 2 AEs was 34 and 88 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 and excluding 2 AEs falling outside the risk window, a total of 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.

15.2.18.3 Conclusion

No relevant safety information was identified in these reports to establish a causal association.

No safety signal was identified.

15.3 Additional Safety Topics for Monitoring

The global vaccine safety database was queried for the cumulative period up to 19-Dec-2022 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 15.3.1)
- Pregnancy (refer to Section 16.8)
- Vaccine anxiety-related reactions (refer to Section 15.3.2)
- Cholecystitis (refer to Section 15.3.3)
- Inflammatory eye disorders (refer to Section 15.3.4)
- Menstrual disorders (refer to Section 15.1.8)
- Paraesthesia (refer to Section 15.1.3)
- Reactogenicity profile- second dose and boosters (based on impurity levels) (refer to Section 15.3.6)

15.3.1 Death, All Cause

Reports with fatal outcome are under surveillance to monitor the frequency and trends in such events.

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

15.3.1.1 Results and Discussion

Nine ICSRs were retrieved for the interval (8 initials and 1 follow-up).

Cumulatively, 9 ICSRs were retrieved (5 males, 4 females, age range 29 – 96 years when reported). The 9 cumulative ICSRs included 23 AEs and the most frequently reported PTs with fatal outcome were AEFI (n=2), Cerebrovascular accident (n=2), Altered state of consciousness (n=1), Cardiac death (n=1), Cardiac disorder (n=1), Cardio-respiratory arrest (n=1), Chest discomfort (n=1), Concomitant disease aggravated (n=1), Death (n=1), and Decreased appetite (n=1).

Appendix 18 includes cumulative line listing of fatal cases received as of 19-Dec-2022.

Following DLP, NVX has received an additional fatal case (between 20-Dec-2022 to 31-Dec-2022) and this additional fatal case was included as part of O/E analysis based on additional exposure data received until 31-Dec-2022.

Results of O/E analyses are presented below.

15.3.1.2 Results of O/E Analysis

The TTO in 6 out of 10 reports with fatal outcome ranged from 0 – 60 days which fell within the risk window of 0 – 60 days (refer to Table 36). TTO was not reported for the other 4 reports and therefore were conservatively included as falling within the risk window. The O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.3.1.3 Conclusion

The reports are confounded by factors such as medical history and/or elderly age of the individuals. A close temporal association was noted in a few reports, however there was insufficient evidence to establish a causal association with NUVAXOVID. All ICSRs met TTO inclusion criteria and results of O/E analyses showed lower than expected rates.

No safety signal was identified.

15.3.2 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).

28 ICSRs were retrieved for the interval (26 initial and 2 follow-up).

Cumulatively, 48 ICSRs were retrieved (5 males, 41 females, 2 individuals of unspecified sex, age range 19 – 65 years when reported). The 48 cumulative ICSRs included 48 AEs (4 serious and 44 non-serious) coded to PTs Anxiety (n=36), Nervousness (n=6), Agitation (n=4), Stress (n=1), and Tension (n=1).

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

No safety signal was identified.

15.3.3 Cholecystitis

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

There were 2 initial ICSRs retrieved for the interval.

Cumulatively, 8 ICSRs were retrieved (3 males, 5 females, age range 38 – 84 years when reported). The 8 cumulative ICSRs included 8 AEs (3 serious and 5 non-serious) coded to PTs Abnormal faeces (n=3), Jaundice (n=2), Blood bilirubin increased (n=1), Faeces pale (n=1) and Gallbladder disorder (n=1).

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.

15.3.4 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).

26 ICSRs were retrieved for the interval (24 initial and 2 follow-up).

Cumulatively, 57 ICSRs were retrieved (11 males, 46 females, age range16 – 72 years when reported). The 57 cumulative ICSRs included 64 AEs (10 serious and 54 non-serious) coded to PTs Eye swelling (n=17), Ocular hyperemia (n=7), Photophobia (n=6), Swelling of eyelid (n=5), Diplopia (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).

No change in the characteristics of this event has been identified following cumulative review. Inflammatory eye disorders will continue to be monitored through routine pharmacovigilance activities. A review of these reports did not reveal a causal association due to insufficient information.

No safety signal was identified.

15.3.5 Herpes Zoster

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

There were 12 initial ICSRs retrieved for the interval.

Cumulatively, 38 ICSRs retrieved (9 males, 26 females, 3 females, 3 individuals of unspecified sex, age range 24 – 76years when reported). The 38 cumulative ICSRs included 40 AEs (4 serious and 36 non-serious) coded to PTs Herpes Zoster (n=37), Herpes Zoster oticus (n=1), Herpes Zoster reactivation (n=1), and Ophthalmic Herpes Zoster (n=1).

15.3.5.1 Results of the O/E Analysis

Parallel sets of O/E and sensitivity analyses were generated for HZ 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.

15.3.5.2 Conclusion

No change in the characteristics of this event following cumulative review. A review of these reports did not reveal a causal association due to insufficient information. HZ will continue to be monitored through routine pharmacovigilance activities.

No safety signal was identified.

15.3.6 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).

35 ICSRs were retrieved for the interval (34 initial and 1 follow-up).

Cumulatively, 111 ICSRs were retrieved for second dose and boosters, 108 of which contained batch numbers (33 males,78 females, age range 20 – 93years when reported). The 111 cumulative ICSRs included 714 AEs (114 serious and 600 non-serious). 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.

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 27, reflective of EU RMP V1.2.

Table 27: Summary of Safety Concerns at the Beginning of the Reporting Interval

Summary of Safety Concerns	
Important identified risk(s)	None
Important potential risk(s)	VAED, including vaccine-associated enhanced respiratory disease (VAERD) Myocarditis and pericarditis
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

Source: EU Risk Management Plan (EU-RMP) V1.2 dated 09-May-2022

On 03-Aug-2022, the signal of myocarditis and pericarditis was confirmed, and a SER was provided in PBRER V 1.0. Upon evaluation of the SER and additional data requested by EMA PRAC, as noted in the PRAC Assessment Report for SSR No.05, the signal of myocarditis and pericarditis was confirmed on 03-Aug-2022 and 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). The risk of myocarditis and pericarditis was renamed to myocarditis and/or pericarditis and reclassified from an important potential risk to an important identified risk in the EU RMP V2.1 of 01-Sep-2022. On 01-Dec-2022, EU RMP V2.1 was approved by EMA.

A summary of the important safety concerns at the end of the reporting interval is provided in, Table 28 consistent with EU RMP V2.1.

Table 28: Summary of Safety Concerns at the End of the Reporting Interval

Summary of Safety Concerns	
Important identified risk	Myocarditis and/or pericarditis
Important potential risk	VAED, including vaccine-associated enhanced respiratory disease (VAERD)
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

Source : EU RMP v 2.1 dated 01-Sep-2022.

16.2 Signal Evaluation

During the reporting interval diarrhoea, dyspnoea and tinnitus underwent signal evaluation. In addition, signals of Anaphylaxis, Myocarditis/pericarditis, Paraesthesia/hypoaesthesia, Chest pain/chest discomfort, Dizziness, Encephalitis/encephalomyelitis, Syncope, Menstrual disorders, Tachycardia and other rhythm abnormalities, Acute coronary syndrome associated with hypersensitivity, were closed following signal evaluation.

Anaphylaxis, myocarditis/pericarditis, paraesthesia/hypoaesthesia signals have been confirmed and product information was updated via safety variation procedures. Myocarditis/pericarditis was reclassified from an important potential risk to an important identified risk in core (EU) RMP V 2.1.

CCDS update is planned for tinnitus.

Analyses of new, ongoing and closed signals are presented in Section 15.1

The subsections are presented below:

- New information on important potential risks – Section 16.3
- New information on important identified risks – Section 16.4
- New information on other potential risks not categorised as important – Section 16.5
- New information on other identified risks not categorised as important – Section 16.6
- Update on missing information: Use in Pregnancy and While Breastfeeding – Section 16.8
- Update on missing information: Use in immunocompromised – Section 16.9
- Update on missing information: Use in frail patients with comorbidities – Section 16.10

- Update on missing information: Use in patients with autoimmune or inflammatory disorders – Section 16.11
- Update on missing information: Interaction with other vaccines – Section 16.12
- Update on missing information: Long term safety – Section 16.13

16.3 New Information on Important Potential Risks

16.3.1 Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD.

16.3.2 Methodology

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

16.3.3 Conclusion

During the reporting interval and cumulatively, no ICSRs were retrieved.

16.4 New Information on Important Identified Risks

During the reporting interval and cumulatively, myocarditis and/or pericarditis was updated to an important identified risk(s) for NVX-CoV2373.

16.4.1 Myocarditis and 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.

The EU SmPC variation to include myocarditis and pericarditis was approved on 25-Oct-2022. A detailed analysis of this topic is presented in Section 15.1.2.

16.5 New Information on Other Potential Risks Not Categorised as Important:

N/A (All potential risks in the reporting interval are classified as important potential risks).

16.6 New Information on Other Identified Risks Not Categorised as Important:

During the reporting interval and cumulatively, there were no identified risks for NVX-CoV2373 not catergorised as important.

16.7 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).

The following definition of vaccination failure was followed to assess the cases:

- Confirmed vaccination failure: occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated by taking into account the incubation period (7 or more days after completing the full dose schedule) and the normal delay for the protection to be acquired as a result of immunisation. This definition requires clinical and laboratory confirmation that the disease is the specifically targeted by the vaccine (e.g., COVID-19 PCR positive test, antigen test).
- Suspected vaccination failure: occurrence of the disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease taking into account the incubation period (7 or more days after completing the full dose schedule) and the normal delay for the protection to be acquired as a result of immunisation.
- Not a vaccination failure: occurrence of the disease in patients who have not received the full dose schedule or occurrence of the disease during the incubation period.

16.7.1 Results and discussion

Six initial ICSRs were retrieved for the interval.

Cumulatively, 7 ICSRs were retrieved (2 males, 5 females, age range 27 – 69 years when reported). The 7 cumulative ICSRs included 7 AEs coded to PTs Vaccination failure (n=6) and Paradoxical drug reaction (n=1). Of the 7 AEs, 5 AEs were designated serious due to IME criteria and 2 AEs were non-serious.

16.7.2 Conclusion

No safety signal was identified.

16.8 Update on Missing Information: Use in Pregnancy and While Breastfeeding

There is limited experience with use of NVX-CoV2373 in pregnant women. It is unknown whether NVX-CoV2373 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).

16.8.1 Results and Discussion

Use in Pregnancy:

Three initial ICSRs were retrieved for the interval.

Cumulatively, 7 ICSRs were retrieved (7 females, age range 23 – 57 years when reported). The 7 cumulative ICSRs included 16 AEs. 6 ICSRs had pregnancy associated AEs which were coded to PTs Abortion spontaneous (n=4) and Maternal exposure during pregnancy (n=2). These 16 AEs included 4 serious and 12 non-serious AEs.

Of these 7 reports, 3 reports were retrospective in nature. In one report, a female at one month gestation, presented with paraesthesia 2 days after vaccination and subsequently experienced spontaneous abortion 2 weeks later. No other significant details were provided in this report. For all other ICSRs, an analysis could not be performed as timing of gestational age, obstetric details, medical history, concomitant medication, and further details were unknown. The TTO ranged from 0 – 33 days when reported (n=7). Further discussion of these ICSRs is found in Section 15.2.16.

Use while breastfeeding:

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

No ICSRs were retrieved for the interval.

Cumulatively, 2 ICSRs were retrieved (2 females, ages 30 and 38 years, respectively). The 2 cumulative ICSRs included 2 AEs coded to PTs Lactation puerperal increased (n=1) and Suppressed lactation (n=1). Both AEs were non-serious.

16.8.2 Conclusion

All the reports of use in pregnancy and use during breastfeeding did not raise any safety concerns.

No safety signal was identified.

16.9 Update on Missing Information: Use in Immunocompromised Patients

NVX-CoV2373 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).

16.9.1 Results and Discussion

Three initial ICSRs were retrieved for the interval.

Cumulatively, 6 ICSRs were retrieved (5 females and 1 male, age range 41 – 93 years when reported). The 6 cumulative ICSRs included 24 AEs including 1 serious and 23 non-serious AEs. Most of the PTs like, Abnormal Sensation in the eyes (n=2), Taste disorder (n=2), Guillain-Barre syndrome (n=1), Herpes zoster (n=1), Muscle twitching (n=1), Paraesthesia (n=1), and Peripheral swelling (n=1) in these immunocompromised patients were nervous system related.

The TTO for all 6 ICSRs ranged from 1 – 22 days.

The reports involved other medical history of polyneuropathy, rhabdomyosarcoma, breast cancer, chemotherapy, hyperthermia therapy, radiotherapy, surgery, gluten sensitivity, coeliac disease, hereditary spherocytosis, splenectomy, cholecystectomy, fibromyalgia, osteoporosis, and lymphoedema.

16.9.2 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.

16.10 Update on Missing Information: Use in Frail Patients with Comorbidities (e.g., Chronic Obstructive Pulmonary Disease [COPD], Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

NVX-CoV2373 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., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (refer to Appendix 13).

16.10.1 Results and Discussion

239 ICSRs were retrieved for the interval (221initial and 18 follow-up).

Cumulatively, 467 ICSRs were retrieved (344 females, 115 males, 8 individuals of unspecified sex, age range 17 – 96 years when reported). The 467 cumulative ICSRs included 2,113 AEs including 426 serious (including 10 fatal AEs) and 1,687 non-serious AEs. The most frequently reported PTs were Dizziness (n=57), Chest pain (n=47), Dyspnoea (n=42), Paraesthesia (n=40) and Tachycardia (n=34). Most reports were of individuals above the age of 40 years

(n=328, 70.23%). The outcome of majority of events was reported as not recovered at the time of reporting (n=804, 38.05%).

16.10.2 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.

16.11 Update on Missing Information: Use in Patients with Autoimmune or Inflammatory Disorders

There is limited information on the safety of the NVX-CoV2373 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).

16.11.1 Results and Discussion

66 ICSRs were retrieved for the interval (58 initial and 8 follow-up).

Cumulatively, 166 ICSRs were retrieved (146 females, 20 males, age range 21 – 94 years when reported). The 166 cumulative ICSRs included 855 AEs including 186 serious (including 8 fatal AEs) and 669 non-serious AEs. The most frequently reported PTs were Headache (n=52) and Fatigue (n=37). Most reports were of individuals above the age of 40 years (n=656, 76.72%). The outcome of the majority of events was reported as not recovered at the time of reporting (n=351, 41.05%).

16.11.2 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.

16.12 Update on Missing Information: Interaction with Other Vaccines

There is limited information on the safety of the NVX-CoV2373 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.

16.12.1 Results and Discussion

No ICSRs were retrieved for the interval.

Cumulatively, 1 ICSR was retrieved (female, age unspecified). The single ICSR included 5 AEs coded to PTs Drug interaction (n=1), Hypertension (n=1), Muscle spasms (n=1), Muscular weakness (n=1), and Tachycardia (n=1). This AE was non-serious.

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.

16.12.2 Conclusion

During the reporting interval and cumulatively, no new information determining interaction with other vaccines was identified.

No safety signal was identified.

16.13 Update on Missing Information: Long-Term Safety

Understanding of the long-term safety profile of NVX-CoV2373 is currently limited.

Long-term safety is evaluated by routine monitoring of Post-Authorisation Safety Studies (PASS).

16.13.1 Results and Discussion

No patients have been enrolled in the current PASS studies since the authorisation of NVX-CoV2373.

16.13.2 Conclusion

During the reporting interval and cumulatively, no new information determining long-term safety was identified.

16.14 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 2.1 that was approved on 01-Sep-2022.

16.15 Effectiveness of Risk Minimisation

Routine risk minimisation measures are in place for NVX-CoV2373; there are no additional risk minimisation measures in place for NVX-CoV2373. All new and closed signals during the reporting interval are evaluated in Section 15.1 and described in the PBRER, including if a product label update is warranted.

17 BENEFIT EVALUATION

17.1 Important Baseline Efficacy/Effectiveness Information

NUVAXOVID is a recombinant, adjuvanted protein vaccine indicated for active immunisation to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The efficacy of NVX-CoV2373 has been established in 2 pivotal Phase III studies, supported by pre- and post-crossover study designs. Pooled efficacy conclusions from the interim and final analysis of two pivotal Phase III randomised, double-blind, placebo-controlled trials evaluating the efficacy, safety, and immunogenicity of two-dose regimen of NVX-CoV2373 administered 21 days apart in adults and adolescents and final analysis in adults (2019nCoV302), interim analysis in adults, adolescent's booster and adult's booster (2019nCoV-301) are summarised below:

- Overall NVX-CoV2373 prevented PCR confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) healthy and clinically stable adult subjects at baseline when the B.1.1.7 (Alpha) variant of SARS-CoV-2 was predominant, with VEs of nearly 90% within a median surveillance time of nearly 2 months and of nearly 83% within a median surveillance time of nearly 4 months.
- In adults, final analysis of the primary efficacy endpoint in the initial vaccination period, with a median surveillance time of 56.0 days, in support of EUA met prespecified study success criterion in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 89.7%
- In adults, final analysis of the primary efficacy endpoint in the initial vaccination period, with a median surveillance time of 101.0 days, in support of BLA met prespecified study success criterion in in serologically negative (to SARS-CoV-2) adult subjects at baseline with a VE of 82.6%
- In adults, relative VE of NVX-CoV2373 to protect against PCR-confirmed mild, moderate, or severe COVID-19 with onset from 7 days after second vaccination in the blinded crossover vaccination period in serologically negative (to SARSCoV-2) at baseline 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%.
- In adults, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to a SARSCoV-2 variant considered or not considered a VOC or VBM with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2). VE of 96.57% due to a SARS-CoV-2 variant not considered as a VOC or VBM and VE of 93.26% due to a SARS-CoV-2 variant considered as a VOC or VBM.
- In adults, a single booster dose of NVX-CoV2373, administered at 8.1 months and 11.2 months after the second dose (primary series) of NVX-CoV2373, elicited robust immune responses against the ancestral Wuhan strain at 28 days after booster vaccination that were higher than those reported at 14 days after primary series vaccination. Noninferiority was achieved for the ratio of neutralising antibody GMTs (GMFR). Higher

immune responses (neutralising antibody and serum IgG antibody) were seen after the single booster dose against the Omicron BA.1 variant in a subset of subjects.

- In adolescents, a single booster dose of NVX-CoV2373 administered to subjects 12 to < 18 years elicited robust immune responses against the ancestral Wuhan strain at 28 days after booster vaccination that were higher than those reported at 14 days after the second dose of NVXCoV2373 of the primary vaccination series.
- In adolescents, a robust serum IgG antibody response against the SARS-CoV-2 spike protein (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series.
- In adolescents, a robust hACE2 receptor binding inhibition to SARS-CoV-2 rS (ancestral Wuhan strain) at 28 days after the third (booster) dose of NVX-CoV2373 was higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series.
- In adolescents, a single booster dose of NVX-CoV2373 after the second dose (primary series) of NVX-CoV2373 in adolescent subjects elicited a robust pseudovirus-based neutralising antibody (ID_{50}) response against the SARS-CoV-2 spike protein (Omicron BA.4/5 Variant) at 28 days after the third (booster) dose of NVX-CoV2373 that was also higher than that reported at 14 days after the second dose of NVX-CoV2373 of the primary vaccination series
- Long term follow-up data are not currently available and safety and efficacy of NVXCoV2373 has not been studied in pregnant and breastfeeding women, immunocompromised patients (except PLWH) and patients with autoimmune or immunodeficiencies. Post-authorisation data will further characterise this missing information.

17.2 Newly Identified Information on Efficacy/Effectiveness

No newly identified information related to efficacy and effectiveness of NVX-CoV2373 was identified during the reporting interval.

17.3 Characterisation of Benefits

Evidence from the final and interim analysis of the two pivotal Phase III CTs suggested that NVX-CoV2373 was shown to be safe and effective in preventing PCR confirmed COVID-19 infection, when a two-dose series was administered 21 days apart in adults and as a booster administered approximately 6 months after completion of the primary series in adolescents and adults.

NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects.

Administration of a third (booster) dose of NVX-CoV2373 to adolescents 12 to < 18 years of age following 2 doses of NVX-CoV2373 in the primary vaccination series met noninferiority criteria

for the humoral immune response, provided robust responses for IgG antibody against the spike protein (ancestral Wuhan strain and the Omicron BA.1 Variant) and for hACE2 receptor binding inhibition and provided robust responses for pseudovirus-based neutralisation antibody responses against the spike protein (Omicron BA.4/5 Variant).

18 INTEGRATED BENEFIT RISK ANALYSIS

18.1 Benefit-Risk Context - Medical Need and Important Alternatives

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. As per World Health Organisation (WHO), through the end of the reporting period, more than 651 million confirmed cases of COVID-19, including 6.6 million deaths, have been reported globally since January 2020.

As of 13-Dec-2022, more than 13 billion vaccine doses have been administered globally. Several VOC (Alpha, Delta, Omicron etc.) have emerged since the original Wuhan strain, which are more transmissible and can cause severe disease or spread more rapidly. 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 interim analysis from 2 pivotal Phase III CTs, NVX-CoV2373 has demonstrated high efficacy in preventing PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to SARS-CoV-2 with onset from at least 7 days after second vaccination in serologically negative adult and adolescent subjects. No subject in the NVX-CoV2373 study arm had PCR-confirmed symptomatic moderate or severe COVID-19 requiring hospitalisation, ICU admission, or mechanical ventilation with onset from at least 7 days after second vaccination in the initial analyses for the studies. In both pivotal Phase III studies, the frequency of Grade 3 solicited local and systemic TEAEs were low but inclined to occur at a higher frequency in the NVX-CoV2373 group than in the placebo group. In both studies, very few subjects reported Grade 4 solicited local and systemic TEAEs.

The benefits of NUVAXOVID have been established across the clinical development program and remain unchanged from the date of first marketing authorisation as reflected in the current global labelling.

For the cumulative period up to 19-Dec-2022, signals of anaphylaxis, myocarditis/or pericarditis and paraesthesia/hypoaesthesia have been confirmed and the CCDS has been updated to include anaphylaxis in Section 4.4 (Special Warnings and Precautions for Use) and paraesthesia/hypoaesthesia in Section 4.8 (Undesirable Effects)and Myocarditis and Pericarditis in Section 4.4 (Special Warnings and Precautions for Use) and Section 4.8 (Undesirable effects) and Paraesthesia/hypoaesthesia in Section 4.8 (Undesirable effects).

On 01-Sep-2022, the core (EU) RMP was updated to reclassify myocarditis and pericarditis from an important potential risk to an important identified risk. The EU RMP was approved on 01-Dec-2022. 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.

Following the DLP, tinnitus was confirmed and CCDS update is planned.

Based on the cumulative safety data received from clinical trials and post-authorisation as of 19-Dec-2022 and with respect to the efficacy of NUVAXOVID in preventing COVID-19 infection caused by SARS-CoV-2, the overall benefit-risk balance of NUVAXOVID remains positive.

19 CONCLUSION

During the reporting interval, NVX has received additional authorisations for adults, adolescents, homologous and heterologous booster indications. Anaphylaxis, myocarditis and pericarditis were added to Special Wand Precautions and paraesthesia/hypoaesthesia were added as undesirable side effects in the CCDS and in updates to the IB and the SmPC.

Myocarditis was re-classified from an important potential risk to an important identified risk in the core RMP.

New signals of diarrhoea, dyspnoea, syncope, menstrual disorders, tachycardia with other rhythm abnormalities, were refuted and SERs are appended to this report. The signal of tinnitus has been confirmed and the SER is appended to this report.

The clinical evidence and post-authorisation safety data collected as of the DLP support the safety and tolerability of NVX-CoV2373. 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.

The overall benefit-risk profile of NVX-CoV2373 remains positive.