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(s) of authorisation	Marketing Authorisation Holder
NUVAXOVID™	EMEAA/H/C/005808	20-Dec-2021	Novavax CZ a.s

AUTHORISATION PROCEDURE in the EU: Conditional Marketing Authorisation

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

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

INTERVAL COVERED BY THIS REPORT: 20-Dec-2021 to 19-Jun-2022

Date of Report: 16-Aug-2022

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

Novavax CZ a.s.
Bohumil 138
Jevany, 28163
Czechia

NAME AND CONTACT DETAILS OF THE QPPV:

Dr. Julia Appelskog
Novavax AB
Kungsgatan, 109
SE-753 18 Uppsala
Sweden

Phone: 4.1(b) [redacted]
E-mail: 4.1(b) [redacted]; qppv@novavax.com

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	4.1(b)
APPROVED BY:	4.1(b) Global Vaccine Safety	
APPROVED BY:	4.1(b) Global Vaccine Safety	

EXECUTIVE SUMMARY

Introduction

This is the first Periodic Benefit-Risk Evaluation Report (PBRER) for NVX-CoV2373 Coronavirus disease (COVID-19) Vaccine (recombinant, Spike Protein, 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 safety data received by Novavax (herein referred to as NVX) for the interval covering 20-Dec-2021 to 19-Jun-2022.

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

Medicinal Product

NVX-CoV2373 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) in individuals aged 18 years of age and older (authorised as COVOVAX in India for ages 7 and older and Thailand for ages 12 and older). In Australia, it (authorised as NUVAXOVID) has also been approved as a booster in adults 18 years of age and older and in New Zealand (authorised as NUVAXOVID) as a heterologous and homologous booster. NVX-CoV2373 is a purified full-length SARS-CoV-2 recombinant (r) 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 2 vaccine components elicit B-cell and T-cell immune responses to the S protein, including neutralising antibodies, which may contribute to protection against COVID-19. One dose (0.5 milliliters [mL]) contains 5 micrograms (µg) of the SARS-CoV-2 rS protein (produced by recombinant deoxyribonucleic acid [DNA] technology using a Baculovirus expression system in an insect cell line that is derived from Sf9 cells of the *Spodoptera frugiperda*) 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. NVX-CoV2373 is supplied in a multidose container 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. NVX-CoV2373 is administered intramuscularly (IM) as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose. 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 (authorised as NUVAXOVID and COVOVAX) have been granted authorisation(s) in the countries and regions in the table below. To fulfil Pharmacovigilance (PV) requirements by country/regional health authorities (HA), 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) and Serum Institute of India Pvt. Ltd. (SIIPL; Indonesia, Philippines, World Health Organisation [WHO], India, Bangladesh, and Thailand).

Country	Authorisation Type	Authorisation / Approval Date	Partner Name / MAH
Indonesia	EUA	31-Oct-2021	SIIPL
Philippines	EUA	17-Nov-2021	SIIPL
WHO	EUL	17-Dec-2021	SIIPL
WHO	EUL	20-Dec-2021	NVX CZ
EU	CMA	20-Dec-2021	NVX CZ
UAE	EUA	26-Dec-2021	GULF MED MEDICINES L.L.C.
India	EUA Adult ≥ 18 years	28-Dec-2021	SIIPL
South Korea	BLA	12-Jan-2022	SK Bioscience Co., Ltd.
Australia	Provisional Registration	20-Jan-2022	Biocelect Pty Ltd.
UK	CMA	03-Feb-2022	NVX CZ
Singapore	Interim Authorisation (PSAR)	03-Feb-2022	PharmEng Technology Pte Ltd.
New Zealand	Provisional Consent	04-Feb-2022	Biocelect New Zealand Ltd.
Canada	NDS	17-Feb-2022	NVX Inc
Bangladesh	EUA	22-Feb-2022	SIIPL
India	EUA Adolescents ≥ 12 to < 18 years	09-Mar-2022	SIIPL
Thailand	EUA	22-Mar-2022	SIIPL
Switzerland	CMA	12-Apr-2022	Future Health Pharma GmbH
Japan	J-NDA	19-Apr-2022	Takeda
Thailand	EUA Adolescents ≥12 to <18 years	11-May-2022	SIIPL
Australia	Provisional Registration (Booster)	09-Jun-2022	Biocelect Pty Ltd
New Zealand	Provisional Consent (Heterologous and Homologous Booster)	17-Jun-2022	Biocelect Pty Ltd

Changes to Reference Safety Information

The Reference Safety Information (RSI) in effect at the beginning of the reporting interval was the European Union Summary of Product Characteristics (EU SmPC) Version (V) 1.0, effective date 20-Dec-2021.

During the reporting interval, the RSI was updated to the Company Core Data Sheet (CCDS) V 1.0, effective date 01-Mar-2022. Subsequently, the CCDS had two version updates to include the adolescent indication and homologous booster dose following its two-dose primary series, respectively. The CCDS in effect at the end of reporting interval was V3.0, effective date 03-May-2022, and was used for assessing ICSRs.

Summary of Clinical Trials

During the reporting interval, there were 6 ongoing NVX clinical trials (CTs): 2019nCoV-101 (Part 2), 2019nCoV-301, 2019nCoV-302, 2019nCoV-311, 2019nCoV-501 and 2019nCoV-505. One CT (2019nCoV-101, Part1) was completed during this reporting interval.

Clinical Trial Exposure

Cumulatively, a total of 44,823 subjects were exposed to at least one dose of NVX-CoV2373 from ongoing and completed CTs.

Post-Authorisation Exposure

Cumulatively, as of 19-Jun-2022, 1,034,110 NVX-CoV2373 doses were administered in Australia, Canada, EU, Japan, New Zealand, and South Korea and a total of 49,230,380 NVX-CoV2373 doses (40,010,380 NUVAXOVID and 9,220,000 COVOVAX doses) were distributed globally.

Overview of Individual Case Safety Reports

During the reporting interval and cumulatively, the number of individual case safety reports (ICSRs) received were as follows:

A total 1874 spontaneous ICSRs were received during the 6-month reporting interval (of which 508 ICSRs contained follow-ups), with a total of 7857 adverse events (AEs) (767 serious unlisted AEs, 261 serious listed AEs, 3808 non-serious unlisted AEs, and 3021 non-serious listed AEs). There was 1 fatal ICSR reported (MedDRA PT: Concomitant disease aggravated).

Routine Monitoring

Qualitative and quantitative methods are employed for surveillance across interval and cumulative data and for the pre-specified AESI And additional safety topics described below.

AESI

Pre-specified AESIs are under routine surveillance for the pandemic setting and signal generations 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. For this 6-month reporting interval, cumulative O/E analyses were also performed up to the cutoff date of 19-Jun-2022.

- Acute Disseminated Encephalomyelitis
- Anaphylaxis
- Autoimmune Thyroiditis
- Bell's Palsy
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Fibromyalgia
- Foetal Growth Restriction
- Generalised Convulsions
- Gestational Diabetes
- Guillain-Barré Syndrome
- Haemorrhagic Stroke
- Ischaemic Stroke
- Kawasaki's Disease
- Major Congenital Anomalies
- Maternal Death
- Microcephaly
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Myasthenia Gravis
- Myocardial Infarction
- Myocarditis
- Myocarditis and Pericarditis
- Pericarditis
- Narcolepsy
- Neonatal Death
- Optic Neuritis
- Postural Orthostatic Tachycardia Syndrome
- Preeclampsia
- Preterm Birth
- Rheumatoid Arthritis
- Spontaneous Abortion
- Stillbirth
- Sudden Death
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Transverse Myelitis
- Vaccine-Associated Enhanced Disease
- Venous Thromboembolism

Other Safety Topics

Other pre-specified safety topics under routine surveillance include:

- Fatal reports
- Experience in special patient populations (paediatric, elderly age groups, pregnancy)
- Vaccine anxiety-related reactions
- Cholecystitis
- Inflammatory eye disorders

- Menstrual disorders
- Paraesthesia
- Reactogenicity profile - second dose and boosters (based on impurity levels)

Overview of Signals: New, Ongoing, or Closed

Following the data lock point, Signal Evaluation Reviews (SERs) were completed for the validated signals of anaphylaxis, myocarditis/pericarditis and paraesthesia/hypoaesthesia for NVX-CoV2373. The signals of anaphylaxis and paraesthesia/hypoaesthesia have been confirmed; myocarditis/pericarditis was assessed and classified as an indeterminate signal at cut-off date and remained an important potential risk until confirmed as an important identified risk on 03-Aug-2022.

Pursuant to HA inquiries received during the reporting interval, the prespecified AESI of encephalitis/encephalomyelitis and the MedDRA PTs of Chest pain/Chest discomfort and Dizziness became validated signals. These signals have been refuted based on lack of evidence supporting a causal association with NVX-CoV2373.

Summary Evaluation of Important Risks and New Information

During the reporting interval and cumulatively, there were no new important identified or potential risks for NVX-CoV2373.

Signal and Risk Evaluation

Following data cut-off, signal evaluations were performed for the validated signals of anaphylaxis, myocarditis/pericarditis, paraesthesia/hypoaesthesia, encephalitis/encephalomyelitis, chest pain/chest discomfort and dizziness for NVX-CoV2373.

Overall Benefit-Risk Analysis Evaluation

The Clinical benefit demonstrated in clinical trials, combined with overall safety profile of NVX -CoV2373 has established a positive benefit-risk profile for the approved indication.

In CTs, administration of NVX-CoV2373, with or without Matrix-M adjuvant was well tolerated in ages 12 years and above. No new safety and efficacy related findings have been observed from CTs that could potentially have a negative impact on subjects enrolled in CTs.

During the reporting interval, Nuvaxovid has been approved for homologous and heterologous in Australia and New Zealand [Booster data summary]

Six signals from the post-authorization setting were validated and reviewed during the reporting interval. Anaphylaxis and paraesthesia/hypoaesthesia were confirmed and CCDS has been updated. Clinical documents will be updated as warranted.

On 03-Aug-2022 (post cut-off date), the validated signal of myocarditis/pericarditis was confirmed and will be reclassified from an important potential risk to an important identified risk. The CCDS and core RMP will be updated accordingly, and a safety variation will be submitted to update the SmPC.

Signals of chest pain/chest discomfort, dizziness and encephalitis/encephalomyelitis have been refuted as signals.

Safety data received during this reporting interval from clinical trials and post-authorisation sources do not indicate any change to the positive benefit-risk balance of NVX-CoV2373.

Conclusion

At the end of the reporting interval, there are no important identified risks for NVX-CoV2373 as described in the EU Risk Management Plan (EU RMP) V1.2 (undergoing HA review). 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 minimization measures.

The CCDS V3.0 at the end of reporting interval describes the safety profile of NVX-CoV2373, and no changes to the RSI were made based on the available safety data as of DLP of this PBRER. CCDS, core RMP and the SmPC will be made pursuant to reclassification of myocarditis/pericarditis as an important identified risk on 03-August-2022.

NVX will continue to monitor all CT and spontaneous post-marketing data including monitoring of all AESIs and other safety topics as part of ongoing pharmacovigilance activities.

The overall benefit-risk balance for NVX-CoV2373 remains favourable.

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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
ADR	Adverse Drug Reaction(s)
AESI	Adverse Event(s) of Special Interest
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
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
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)
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
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
HCP	Healthcare Professional
HCW	Healthcare Worker
HGLT	High Level Group Term
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IBD	International Birth Date
ICC	Influenza COVID Combination
ICD	International Classification of Disease
ICSR	Individual Case Study Report

Acronym	Abbreviation Definition
ICU	Intensive Care Unit
IDI	Integrated Data Infrastructure
IgG	Immunoglobulin G
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
MSSO	Maintenance and Support Services Organization
MVD	Medical Data Vision Co. Ltd (MVD
NA or N/A	Not Available or Not Applicable
NDS	New Drug Submission
NHS	National Hauora Coalition
NMDS	National Minimum Data Set

Acronym	Abbreviation Definition
No.	Number
NS	Non-Serious
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSL	Non-Serious Listed
NSUL	Non-Serious Unlisted
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
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)
PV	Pharmacovigilance
PVA	Pharmacovigilance Agreement(s)
qNIV	Quadrivalent Nanoparticle Influenza Vaccine
ROR	Reporting Odds Ratio
Rr	Reporting Rate
RR	Rate Ratio
RSI	Reference Safety Information
S	Spike
SAE	Serious Adverse Event(s)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SC	Subcutaneous

Acronym	Abbreviation Definition
SER	Signal Evaluation Review
SIIPL / SII	Serum Institute of India PVT. LTD.
SL	Serious Listed
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPEAC	Safety Platform for Emergency vACcines
SSR	Summary Safety Report
ST	Summary Tabulation(s)
SUL	Serious Unlisted
SVA	Swedish National Veterinary Institute
TEAE	Treatment Emergent Adverse Event
TGA	Therapeutic Goods Administration
TTO	Time to Onset
TTS	Thrombosis and Thrombocytopenia Syndrome
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
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 first 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 (herein referred to as NVX) global vaccine safety database from worldwide sources for the period covering 20-Dec-2021 to 19-Jun-2022.

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

NVX-CoV2373 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) in individuals aged 18 years of age and older (authorised as COVOVAX in India for ages 7 and older and Thailand for ages 12 and older). In Australia, it (authorised as NUVAXOVID) has also been approved as a booster in adults 18 years of age and older and in New Zealand (authorised as NUVAXOVID) as a heterologous and homologous booster. NVX-CoV2373 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 2 vaccine components elicit B- and T-cell immune responses to the S protein, including neutralising antibodies, which may contribute to protection against COVID-19. One dose (0.5 milliliters [mL]) contains 5 micrograms (µg) of the SARS CoV2 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*) 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. NVX-CoV2373 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. NVX-CoV2373 is administered intramuscularly (IM) as a course of 2 doses of 0.5 mL each. It is recommended to administer the second dose 3 weeks after the first dose.

Further details on the mechanism of action, indications, pharmaceutical form(s) and instructions for use are presented in the CCDS (refer to Appendix 2).

Refer to Appendix 15 for Australian-specific regional requirements; Appendix 16 for Canadian-specific requirements; Appendix 17 for EU-specific requirements; and Appendix 18 for United Kingdom (UK) specific requirements.

2 WORLDWIDE MARKETING AUTHORISATION STATUS

NVX-CoV2373 is currently authorised in multiple regions for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. In India and Thailand COVOVAX is authorised for individuals aged 7 and older and,12 and older respectively. In Australia, it has been approved for a booster in adults 18 years of age and older and in New Zealand as a heterologous and homologous booster.

To fulfil pharmacovigilance (PV) requirements by country/regional HAs, NVX entered into Pharmacovigilance Agreements (PVAs) with Biocelect (Australia, New Zealand), SK Bioscience (South Korea), PharmEng Technology Pte Ltd. (Singapore), and Serum Institute of India Pvt Ltd. (SIIPL), (Indonesia, Philippines, World Health Organisation [WHO], India, Bangladesh, and Thailand). 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 European Union Summary of Product Characteristics (EU SmPC) Version (V) 1.0 effective date 20-Dec-2021 (refer to Appendix 1).

4.1 Variation Procedures

The following variation procedures are ongoing or completed during the reporting interval.

- Adolescent variation: Submitted 29-Mar-2022, Approved 01-Jul-2022
- SK Bio – DS Manufacturer: Submitted 30-Apr-2022, Approved 04-Jul-2022
- Omicron variation: Submitted 13-Apr-2022, Under Review
- Homologous and Heterologous Boost variation: Submitted 17-May-2022, Under Review
- Shelf-life Extension (9 to 11 months) variation: Submitted 09-Jun-2022, Under Review

4.2 Company Core Data Sheet (CCDS)

During the reporting interval, the RSI was updated to the Company Core Data Sheet (CCDS) V 1.0, effective date 01-Mar-2022. Subsequently, the CCDS had two version updates to include the adolescent indication and homologous booster dose following its two-dose primary series respectively. The current CCDS in effect, is V3.0, effective date 03-May-2022, and it was used

for assessing ICSRs in the global vaccine safety database (refer to Appendix 2). A summary of changes between the versions is presented below.

Table 1: CCDS Summary of Changes

Version Number	Approval Date	Summary of Changes
V1.0	01-Mar-2022	Initial Version
V2.0	21-Mar-2022	Changes in CCDS from V1.0 to V2.0 Therapeutic indication: Age specification under indication was updated from "18 years of age and older" to "12 years of age and older" to include adolescent population in the indication statement. Dosing and method of administration: Dosing and schedule was updated to clarify that there was one dosing regimen for both adolescent and adult populations. The age range of special population was updated to "children 12 years of age and older". Undesirable effects: Supporting data was added about safety in adolescents 12 through 17 years of age. Pharmacodynamic properties: Clinical efficacy was updated with data supporting efficacy in adolescents 12 through 17 years of age.
V3.0	03-May-2022	Changes in CCDS from V2.0 to V3.0 Posology and method of administration: Instructions of use were added under a new subheading of "Booster dose" and "Individuals 18 years of age and older". Undesirable effects and Pharmacodynamic properties: Studies supporting the addition of homologous booster was added. Editorial changes and other minor adjustments to existing text were made.

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, a total of 44,823 subjects have been exposed to 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 an estimate of cumulative number of subjects exposed to the NVX-CoV2373 from all 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	42,671
Placebo (normal saline)	8,403
ICC (qNIV + NVX-CoV2373)	558
NVX-CoV2515	72
NVX-CoV2373+ NVX-CoV2515	52

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

Table 3: Estimated Cumulative Exposure in Adolescent Subjects

Treatment	Total Number of Subjects Exposed (≥ 12 to < 18 years of age)[b]
NVX-CoV-2373	2,152
Placebo (normal saline)	80

[b]: Includes data from 2019nCoV-301, adolescent sub-study.

Table 4 and Table 5 below present cumulative summary tabulations from completed CTs by demographic data (age, gender, and ethnicity).

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

Age Range[a]	Male	Female	Total
Adults (18-59 Years)	55	53	108

[a]: Includes data from final CSR for 2019nCoV-101 (Part 1) study.

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

[a] Includes data from final CSR for 2019nCoV-101 (Part 1) study.

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

Exposure data are derived from administration records and distribution data. The regional sources of administration and distribution data, including cut-off dates, are presented in Table 6. Administration data stratified by dose, age group and region are provided in Table 7, Table 8,

and Table 9, respectively. Distribution data are provided for all regions that received NUVAXOVID and COVOVAX, including some regions where administration data are also available (refer to Table 9).

Cumulatively, as of 19-Jun-2022, 1,034,110 NVX-CoV2373 doses were administered in Australia, Canada, EU, Japan, New Zealand, and South Korea and a total of 49,230,380 NVX-CoV2373 doses (40,010,380 NUVAXOVID and 9,220,000 COVOVAX doses) were distributed globally (refer to Table 9 for administration and distribution data).

Table 6: Administration and Distribution Sources Data by Country

Country	Administration Data Source	Administration Data Cut-off Date	Distribution Data Source	Distribution Data Cut-off Date
Countries Included in O/E Analysis				
Australia[a]	COVID19VaccineData@Health.gov.au	19-Jun-2022	NVX Distribution Department	19-Jun-2022
Canada[a]	https://health-infobase.canada.ca/covid-19/vaccination-coverage/#a6	19-Jun-2022[c]	NVX Distribution Department	19-Jun-2022
EU[a]	https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea	19-Jun-2022[c]	NVX Distribution Department	19-Jun-2022
Japan[a]	Takeda Pharmaceutical Company	19-Jun-2022	Takeda Pharmaceutical Company	14-Jun-2022
New Zealand[a]	New Zealand Ministry of Health (NZ MoH) provided by license partner, Biocelect, via Biointelect.	31-May-2022	NVX Distribution Department	19-Jun-2022
Singapore[a]	N/A	N/A	NVX Distribution Department	19-Jun-2022
Countries not Included in O/E Analysis				
Bangladesh[b]	http://103.247.238.92/webportal/pages/covid19-vaccination-update.php	N/A	SIIPL's SSR V09 (01-May-2022 to 31-May-2022)	N/A
India[b]	https://dashboard.cowin.gov.in/	23-Jun-2022	SIIPL's SSR V09 (01-May-2022 to 31-May-2022)	N/A
Indonesia[b]	N/A	N/A	SIIPL's SSR V09 (01-May-2022 to 31-May-2022)	N/A
Philippines[b]	https://www.fda.gov.ph/list-of-fda-issued-emergency-use-authorisation/	N/A	SIIPL's SSR V09 (01-May-2022 to 31-May-2022)	N/A
Thailand[b]	N/A	N/A	SIIPL's SSR V09 (01-May-2022 to 31-May-2022)	N/A
South Korea[a]	https://www.kdca.go.kr/board/board.es?mid=a20501020000&bid=0015&list_no=718699&cg_code=C01&act=view&nPage=1	19-Jun-2022	SK Bio Distribution Data	31-May-2022
UAE[a]	N/A	N/A	NVX Distribution Department	N/A
UK[a]	Communication from Vaccine Delivery Team Gov.UK/beis	N/A	NVX Distribution Department	N/A

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 and European Center for Disease Prevention and Control (ECDC). Date presented for Canada and EU in this table is the date of extraction.

Table 7 below provides detailed information pertaining to the actual doses administered, doses assumed to be administered after accounting for doses assumed to be administered based on distribution data (if applicable), and the total estimated number of doses administered by dose and presented for interval and cumulative periods. Only administration data for regions included in the Observed / Expected (O/E) analysis (i.e., Australia, Canada, EU, Japan, New Zealand, and Singapore) are included in this table. A brief description of each column is presented below.

Actual doses administered include administration data available by dose, as received directly from the data source (no adjustments or assumptions have been made). If a country had an administration data source listed, data from that country is included in this column.

Actual administered doses Third/Fourth/Booster/Unknown dose included as Dose 1 and Dose 2 only includes a reallocation of third/fourth/booster doses of NUVAXOVID as recorded by global public health authorities within the context of a COVID-19 vaccine series, independent of specific vaccine administered. This reallocation was made recognising that certain regional vaccination policies recommend the use of NUVAXOVID as a booster dose under certain clinical settings, and given the time on the market, a third/fourth/booster dose of NUVAXOVID was implausible. Reallocation of third/fourth/booster doses was made according to the following ratio: 80% of third/fourth/booster doses to first doses, and 20% to second doses. This reallocation ratio may be adjusted over time.

Calculated doses administered from distribution data includes the assumed number of doses administered as derived from distribution data. Only distribution data from Singapore was used to derive administered doses. The method of calculation used for this redistribution is available in Appendix 10.

Total estimated doses administered includes the summation of the values in the following columns: Actual administered doses with third dose included as Dose 1 and Dose 2 only 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.

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

Dose	Actual Doses Administered[a]	Actual Administered Doses with Third/Fourth/Booster/ Unknown Dose Included as Dose 1 or Dose 2 Only[b]	Calculated Doses Administered (from distribution data)[c]	Total Estimated Doses Administered[d]
First Dose	332,104	701,422	4,677	706,099
Second Dose	269,665	368,602	1,169	369,771
Third/Booster Dose	432,184	0	0	N/A
Unknown Dose	3	0	0	N/A
Cumulative Total[e]	**1,034,110**	**1,070,178**	**5,846**	**1,076,024**

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

[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 Table 6 for a list of countries with administration data.

[b] Column represents administration data re-allocated to first and second dose only (refer to calculations above Table 7, this is used for calculating total estimated administration doses for O/E analysis). All countries with administration data according to Table 6 are presented in this column. For a list of countries for which this re-allocation was applied, refer to text above Table 7.

[c] Column represents 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. The data presented represents the source data provided by Australia and New Zealand.

Table 8: Cumulative Actual Exposure Data (Administered) per Age Group from Post-Authorisation Experience

Total Doses Actually Administered[a]			
Dose	**Paediatrics**	**Adults**	**Elderly**
First Dose	91	93,936	9,148
Second Dose	63	81,345	8,090
Third/Booster Dose	50	50,422	15,013
Cumulative Total	**204**	**225,703**	**32,251**

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 (source presented in Table 6) did not provide age categories consistently as per ECDC data, so this table does not cover all doses from ECDC data.

[c] Age groups under the available age stratification for the EU, Australia and New Zealand is as follows: Paediatric- < 18 years; Adults- 18 – 69 years; Elderly – 70+ years. Japan has Elderly 65+.

[d] Australia and New Zealand had administration data in only adolescent and elderly age groups. Japan has age category available only for age 65+.

Table 9: Interval and Cumulative Exposure Data (Distributed and Administered) from Post-Authorisation Experience Presented by Region/LP

Region / License Partner (LP)	Total Doses Administered[a]	Total Doses Distributed[a]
Australia (Biocelect Pty Ltd.)[b]	156,596	6,864,600
Canada (NVX)[b]	5,448	3,238,100
EU (NVX)[b]	288,489	22,479,990
India[c]	N/A	12,000
Indonesia (SIIPL)[c]	N/A	9,008,000
Japan[b]	17,563	3,641,380
New Zealand (Biocelect New Zealand Ltd)[b]	3,904	1,251,600
Singapore[b]	NA	504,000
South Korea (SK Bioscience)[b]	562,110	2,030,710
Thailand (SIIPL)[c]	N/A	200,000
NUVAXOVID Total	**1,034,110**	**40,010,380**
COVOVAX Total	**N/A**	**9,220,000**

Note: Data Sources and cut-off dates are presented in Table 6.
[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), V24.0 was used for the coding of serious adverse events (SAE) for study 2019nCoV-301. MedDRA V24.1 was used for coding SAEs for studies 2019nCoV-101 (Part 1 and Part 2), 2019nCoV-302, 2019nCoV-501 and 2019nCoV-505. MedDRA V25.0 was used for coding of SAEs for 2019nCoV-311 study.

ADRs received following authorisation were coded using MedDRA V24.1 at the beginning of the reporting interval and V25.0 at the end of reporting interval.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Appendix 4 presents cumulative summary tabulation of serious adverse events (SAEs) from NVX-sponsored interventional 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 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)**, no SAEs or Adverse Events of Special Interest (AESI) have been reported.

In study **2019nCoV-101 (Part 2)**, 44 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 (9 PTs), Cardiac Disorders (7 PTs), Infections and Infestations (7 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (7 PTs), and Gastrointestinal Disorders (6 PTs).

In study **2019nCoV-301**, 894 adult subjects and 24 adolescents who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced a total of 1,536 SAEs. The most frequent SAEs (50 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (364 PTs), Cardiac Disorders (174 PTs), Respiratory, Thoracic and Mediastinal Disorders (128 PTs), Psychiatric Disorders (110 PTs), Injury, Poisoning and Procedural Complications (122 PTs), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (98 PTs), Nervous System Disorders (99 PTs), and Gastrointestinal Disorders (68 PTs).

In study **2019nCoV-302**, 387 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 468 SAEs. The most frequent 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 (47 PTs), Nervous System Disorders (37 PTs), and Gastrointestinal Disorders (78 PTs).

In study **2019nCoV-311**, no subject experienced Treatment Emergent Adverse Event (TEAE) as of DLP of this PBRER.

In study **2019nCoV-501**, 92 subjects who received NVX-CoV2373 with Matrix-M adjuvant or placebo experienced 99 SAEs. End of study unblinding confirmed that 50 SAEs occurred in the vaccine arm and 49 SAEs occurred in the placebo arm. The most frequent SAEs (10 or more PTs) experienced by subjects fall under the SOCs of Infections and Infestations (23 PTs) and Injury, Poisoning and Procedural Complications (15 PTs), and Pregnancy, Puerperium and Perinatal Conditions (10 PTs).

In study **2019nCoV-505**, two serious Treatment Emergent Adverse Events (TEAE) have been reported as of the DLP of this PBRER.

6.3 Cumulative and Interval Summary Tabulations from Post-Authorisation Data

Appendix 5 presents interval and cumulative count of ICSRs. 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.

A total 1874 spontaneous ICSRs were received during the 6-month reporting interval (of which 508 ICSRs contained follow-ups), with a total 7857 AEs (767 serious unlisted AEs, 261 serious listed AEs, 3808 non-serious unlisted AEs, and 3021 non-serious listed AEs). There was 1 fatal ICSR reported.

- Of the 158 medically confirmed ICSRs received during the reporting interval, there were 69 serious ICSRs with 171 unlisted AEs (including 1 AE with fatal outcome) and 52 listed AEs, and 89 non-serious ICSRs containing 230 unlisted and 108 listed AEs.
- Of the 1716 non-medically confirmed ICSRs (reporter is not identified as an HCP) received during the reporting interval, there were 274 serious ICSRs with no fatal outcomes, containing 596 unlisted AEs, and 209 listed AEs, and 1442 non-serious ICSRs containing 3578 unlisted AEs, and 2913 listed AEs.

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.

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

7.1 Completed Clinical Trials

During the reporting interval, one clinical study was completed for NVX-CoV2373, and study details are summarised in Appendix 7 and Table 31. Safety and immunogenicity results from the final Clinical Study Report (CSR) are summarised below.

- There were no SAEs or Adverse Events of Special Interest (AESI) reported throughout the study.
- Solicited local and systemic TEAE accounted for the majority of TEAEs in the study and were predominantly Grade 1 in severity, of relatively short duration (median ≤ 2 days) and occurred at higher frequencies in the 2-dose 5 µg and 25 µg adjuvanted vaccine groups than in the 1-dose 25 µg adjuvanted vaccine, 2-dose 25 µg unadjuvanted vaccine, or placebo groups.
- Pain and tenderness were the most commonly reported solicited local TEAEs.

- Headache, fatigue, and myalgia were the most commonly reported solicited systemic TEAEs.
- Grade ≥ 2 hematologic laboratory abnormalities occurred in 6 participants (4.6%) across most of the active vaccine and placebo groups and consisted of decreased haemoglobin. Grade 3 events occurred in 5 participants (3.8%), and there were no Grade 4 events. These events were predominantly transient in nature.
- Grade ≥ 2 serum chemistry abnormalities occurred in 10 participants (7.6%) across the active vaccine and placebo groups and consisted of increased alanine aminotransferase /aspartate aminotransferase, increased urea, increased bilirubin, and increased sodium. Grade 3 events occurred in 2 participants (1.5%), and there were no Grade 4 events. These events were predominantly transient in nature.
- Grade ≥ 2 vital sign abnormalities occurred in 19 participants (14.5%) across the active vaccine and placebo groups and consisted of changes in blood pressure and pulse rate. Grade 3 events occurred in 7 participants (5.3%), and there were no Grade 4 events. These events were predominantly transient in nature.
- 2-dose regimens of 5 µg and 25 µg SARS-CoV-2 rS with 50 µg Matrix-M adjuvant, administered 21 days apart, induced robust immune responses 2 weeks after second vaccination (Day 35) compared to a 1-dose regimen of 25 µg adjuvanted vaccine, 2-dose regimen of 25 µg unadjuvanted vaccine, and placebo in healthy adult participants 18 to 59 years of age.
- Cell-mediated immune responses for the Th1 and Th2 cytokine pathways were evident in the 2-dose 5 µg and 25 µg adjuvanted vaccine groups, with responses skewed toward the Th1 cytokine pathway.

7.2 Ongoing Clinical Trials

During the reporting interval, 6 NVX-sponsored CTs are ongoing, and an overview of studies are summarised in Appendix 7 and Table 32. There were no emerging safety findings reported from the ongoing CTs. The most recent interim safety, immunogenicity, and efficacy analysis results for ongoing CTs are summarised below.

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 with a paediatric expansion in adolescents (12 to < 18 years) in the US. The data cut-off for the interim efficacy and safety results for the adult portion of the study was 31-May-2021 and excludes data from the blinded cross-over period. The study met the prespecified final primary efficacy outcome measure versus (vs) placebo in preventing polymerase chain reaction (PCR)-confirmed symptomatic mild, moderate, or severe COVID-19 with onset from at least 7 days after second vaccination in serologically negative adult subjects.

- The overall vaccine efficacy (VE) was 90.4%.
- There were no moderate or severe cases of COVID-19 among subjects who received SARS-CoV-2 rS.
- SARS-CoV-2 rS prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to SARS-CoV-2 variant considered or not considered a Variant of Concern (VOC) or Variant of Interest (VOI) with onset from at least 7 days after second vaccination on serologically negative adult subjects.
- SARS-CoV-2 rS 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.
- SARS-CoV-2 rS prevented PCR-confirmed any symptomatic SARS-CoV-2 infection with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects, with results similar to those of the primary efficacy endpoint (VE = 90.55% (95% confidence interval [CI]: 83.16, 94.70).
- Higher frequencies of solicited local and systemic treatment emergent adverse events (TEAE) in the SARS-CoV-2 rS than in the placebo, especially after the second dose. The majority of solicited local and systemic TEAEs were of grade 1 or grade 2 severity and of short duration.
- Frequencies of Grade 3 solicited local and systemic TEAEs were low but tended to occur at a higher frequency in the SARS-CoV-2 rS than in the placebo group. Few subjects reported Grade 4 solicited local and systemic TEAEs. Tenderness and pain were the most frequently solicited local TEAEs. Fatigue, headache, muscle pain, and malaise were the most frequently solicited systemic TEAEs.
- The majority of subjects in the 2 treatment groups reported unsolicited TEAEs that were mild in severity. SAEs were infrequently reported and balanced between the treatment groups. Medically attended adverse events (MAAE) were also balanced between the study groups. Potentially immune medicated medical conditions (PIMMC) by investigator reporting and protocol-defined criteria were balanced between treatment groups.
- No fatal event was assessed as related to SARS-CoV-2 rS, and the events reported were mostly consistent with the morbidity associated with age and underlying medical conditions in the study population.
- No specific treatment related TEAEs led to study discontinuation in either group.

The data cut-off for the interim efficacy and safety results for the **2019nCoV-301 adolescents (≥ 12 to < 18 years)** part of the study was 27-Sep-2021 and excludes data from the blinded cross-over period. The results are summarised below.

- VE was 79.54% for the primary endpoint.

- All cases were mild in severity. There were no moderate or severe cases of COVID19 among SARS-CoV-2 rS or placebo adolescent recipients.
- VE = 82.04% due to a SARS-CoV-2 variant considered as a VOC/VOI, which was represented only by the Delta VOC.
- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from at least 7 days after second vaccination in adolescent subjects. regardless of baseline serostatus with results similar to those of the primary efficacy endpoint
- NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from first injection in adolescent subjects regardless of baseline serostatus.
- Higher frequency of solicited local and systemic TEAEs were observed in the NVX-CoV2373 than in the placebo group, especially after the second dose. The majority of solicited local and systemic TEAEs were of grade 1 or grade 2 severity. Frequency of grade 3 solicited local and systemic TEAEs were low, but mostly observed at a higher frequency in the SARS-CoV-2 rS than in the placebo group. No subject reported grade 4 solicited local or systemic TEAEs. Tenderness and pain were the most frequent solicited local TEAEs. Headache, fatigue, muscle pain, and malaise were the most frequent solicited systemic TEAEs.
- No fatal events occurred in the paediatric expansion at the time of this analysis, and no participant discontinued the study due to a TEAE. There were no PIMMCs or AESIs relevant to COVID-19 in the paediatric expansion. SAEs were infrequently reported and were balanced between the treatment groups. MAAEs and severe MAAEs were also balanced between the study groups.

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. The interim safety, efficacy and immunogenicity following the initial set of vaccinations with a data cutoff date of 27-Jul-2021 are summarised below. The interim results include data from the initial placebo-controlled phase as well as blinded crossover phase that was available at the cutoff date.

- Two-dose regimen of NVX-CoV2373 vs placebo, administered 21 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 adult subjects at the 6-month analysis of the primary endpoint.
- The VE at the 6-month analysis was 82.7% (alpha-adjusted 96.7% CI: 73.3, 88.8; p < 0.0001) with an alpha-adjusted lower bound confidence interval (LBCI) > 30%.

- No participant in the NVX-CoV2373 group and 6 subjects in the placebo group had PCR-confirmed symptomatic severe COVID-19 with onset from at least 7 days after second vaccination.
- The VE was 100% (95% CI: 17.9, 100.0) in preventing PCR (Polymerase chain reaction)-confirmed symptomatic severe COVID-19 in serologically negative adult subjects. No participant in the NVX-CoV2373 group and 1 participant in the placebo group 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.
- Additionally, the VE was 100% (95% CI: 0.000, 37.712) in preventing PCR-confirmed symptomatic moderate or severe COVID-19 requiring hospitalisation, ICU (Intensive care unit) admission, or mechanical ventilation in serologically negative adult subjects.
- A two-dose regimen of NVX-CoV2373 also markedly increased anti-S immunoglobulin G (IgG) and neutralising antibody levels relative to placebo at 2 weeks after the second vaccination (Day 35) regardless of baseline serostatus, with higher levels in the younger adult cohort (18 to 64 years) than in the older adult cohort (65 to 84 years) but with similarly high SCRs.
- 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.
- Tenderness and pain were the most frequent solicited local TEAEs in the 2 study vaccine groups, with 705 (54.9%) and 394 (30.7%) subjects, respectively, in the NVX-CoV2373 group and 223 (17.5%) and 130 (10.2%) subjects in the placebo group. Grade 3 tenderness and pain were reported in 14 (1.1%) and 1 (<0.1%) subject in the NVX-CoV2373 group and 1 (<0.1%) and 1 (<0.1%) participant in the placebo group. Median durations of tenderness and pain were 2.0 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).
- 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 NVX-CoV2373 (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 participant in the placebo group reported Grade 4 events. Headache, fatigue, and muscle pain were the most frequent 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 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.
- 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 due to 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.

Study **2019nCoV-501** is a randomised, observer-blind, placebo-controlled trial evaluating the efficacy, safety, and immunogenicity of a 2-dose regimen of NVX-Cov2373 or placebo administered 21 days apart in South African HIV negative subjects aged ≥ 18 to < 85 years and 233 medically stable PLWH adult subjects aged ≥ 18 to < 65 years old. The Day 236 assessments included analyses of subjects who received a third vaccination (booster) at Day 201 and of subjects who received placebo initially and then crossed over at Day 201 to receive 2 vaccinations of SARS-CoV-2 rS, 21 days apart. Safety was monitored via assessments of unsolicited TEAEs including TEAEs, severe TEAEs, treatment related TEAEs, treatment related severe TEAEs, SAEs, AESI [PIMMCs and COVID-19 related], and MAAEs stratified by baseline serostatus and HIV infection status. The safety and immunogenicity results are summarised below.

- The rate of subjects with unsolicited TEAEs, regardless of baseline serostatus, over the entire study, was lower for NVX-CoV2373 (pre-crossover + post-crossover) vs placebo (pre-crossover).
- The frequency of unsolicited TEAEs among all subjects, regardless of baseline serostatus, following third vaccination (booster – post-crossover) was low and higher overall for NVX-CoV2373 to booster (post-crossover) than it was for placebo to NVX-CoV2373 (post-crossover).
- Most frequent unsolicited TEAEs, respectively, among all subjects, regardless of baseline serostatus, following third vaccination (post-crossover), were injection site pain, injection site swelling, and ageusia (NVX-CoV2373 to booster [post-crossover]).
- Frequency of unsolicited treatment related TEAEs among all subjects, regardless of baseline serostatus, following third vaccination (post-crossover), was low and higher overall for NVX-CoV2373 to booster (post-crossover) vs placebo to NVX-CoV2373 (post-crossover) (0.1%).

- Most frequent unsolicited treatment-related TEAEs, respectively, among all subjects, regardless of baseline serostatus, following third vaccination (post-crossover), were injection site pain and injection site swelling (NVX-CoV2373 to booster [post-crossover]).
- Most unsolicited TEAEs following third vaccination (post-crossover) were mild or moderate in severity.
- The most frequent unsolicited severe TEAEs following third vaccination (booster – post-crossover) were injection site pain, injection site erythema, injection site induration, and renal failure (NVX-CoV2373 to booster [post-crossover]). The most frequent severe treatment-related TEAEs following third vaccination (booster – post-crossover) were injection site pain, injection site erythema, and injection site induration (NVX-CoV2373 to booster [post-crossover]).
- Induced robust immune responses in healthy Human Immunodeficiency Virus (HIV)-negative South African subjects ≥ 18 to < 85 years of age and medically stable persons living with HIV (PLWH) South African subjects ≥ 18 to < 65 years of age.
- Boosted immune responses that had declined over time (i.e., through 201 days after first vaccination), to levels higher than those seen for the initial peak immune response.
- Was well tolerated in healthy HIV-negative South African subjects ≥ 18 to < 85 years of age and medically stable PLWH South African subjects ≥ 18 to < 65 years of age.

Study **2019nCoV-101 (Part 2)** is the second part of a first-in-human randomised, observer-blind, placebo-controlled trial evaluating the safety and immunogenicity of SARS-CoV-2 rS (5 µg and 25 µg) with or without 50 µg Matrix-M adjuvant in 1,283 healthy adult subjects 18 to 84 years of age. The conclusions were based on the Day 217 interim analysis and are summarised below.

- SAEs were reported in 32 (2.5%) subjects overall with Group A (4 [1.6%]), Group B1 (5 [3.3%]), Group B2 (6 [5.7%]), Group C1 (5 [3.3%]), Group C2 (3 [2.9%]), Group D (3 [1.2%]), and Group E (6 [2.4%]) subjects reporting events with similar, low frequencies.
- Up to 3 doses of 5 µg SARS-CoV-2 rS with 50-µg Matrix-M adjuvant administered on Day 0, Day 21, and Day 189, were well-tolerated in healthy adult subjects 18 to 84 years of age.
- Declines in IgG, Angiotensin Converting Enzyme (hACE2) receptor binding inhibition, and neutralising antibody activity titers were observed between Day 35 and Day 189 in subjects initially primed with active vaccine (Group B, Group C, Group E, and Group D).
- A third (booster) dose of 5 µg SARS-CoV-2 rS with 50-µg Matrix-M adjuvant administered 6 months following priming vaccination produced:
- Serum IgG antibody Geometric Mean Titer (GMTs) ~31.3-fold greater than titers at Day 189 and a ~4.7-fold greater than titers reported following priming vaccination,

- hACE2 receptor binding inhibition GMTs ~50.1-fold greater than titers at Day 189 and ~7.2-fold greater than titers following priming vaccination,
- Neutralising antibody activity (MN50) ~86.7-fold greater than titers at Day 189 and ~4.1-fold greater than titers following priming vaccination.
- Two doses of 5 μg SARS-CoV-2 rS with 50-μg Matrix-M over a 6-month dosing interval produced serum IgG, hACE2, and neutralising antibody titers ~2.5-fold, ~4.5-fold, and ~2.1-fold higher than with a 3-week dosing interval.
- Subjects receiving multiple active vaccinations (Group B1, Group B2, Group C2, and Group D) reported solicited local and systemic TEAEs at higher frequencies and with higher intensity with subsequent vaccinations through Dose 1, Dose 2, and Dose 3.
- Overall, a single booster dose of SARS-CoV-2 rS administered approximately 6 months after priming vaccination induced a substantial increase in humoral antibodies that was > 4-fold higher than antibody titers associated with high levels of efficacy in two Phase 3 studies while also displaying an acceptable safety profile.
- Exploratory analysis using Group B2 participant sera demonstrated the single booster dose of SARS-CoV-2 rS administered approximately 6 months after priming vaccination induced substantial increases in humoral antibodies for both the prototype strain and all variants evaluated that were similar to or higher than those associated with high levels of efficacy in Phase 3 studies of the vaccine.

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. No treatment emergent SAEs were reported as of the DLP of this PBRER.

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. No treatment emergent SAEs were reported as of the DLP of this PBRER.

7.3 Long-Term Follow-Up

Subjects enrolled in NVX-sponsored CTs were not subject to long-term safety follow-up.

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, one phase 1/2, randomised, observer-blind study (Study ID: **2019nCoV-ICC-E-101**) to evaluate the safety and immunogenicity of a quadrivalent Nanoparticle Influenza Vaccine (qNIV) and NVX-CoV2373 in healthy subjects ≥ 50 to ≤ 70 years of age is ongoing. No significant safety findings were observed in the ongoing blinded safety review. The final study results were not available as of the DLP of this PBRER.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

No safety findings were reported from any observational, epidemiological, registry and active surveillance programs. During the reporting interval, one Post-authorisation Safety Study (PASS) was ongoing, and no data has been collected or relevant safety information has been received from this study that would impact the benefit-risk assessment of NVX-CoV2373. Appendix 8 provides an overview of ongoing and planned studies.

As per EMA procedure, EMEA/H/C/005808/MEA/00, feasibility assessments are run on a monthly basis for 2019nCoV-402 study to determine, if there are enough patients vaccinated with Nuvaxovid, within the database, to conduct appropriate analysis. As of DLP, Nuvaxovid doses were not distributed in UK to conduct the feasibility assessment.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

During the reporting interval, there was no relevant new safety observations identified from any other studies for 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 broad search strategy SMQ (broad): Medication Errors.

9.2.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 43 ICSRs meeting the prespecified search strategy for medication errors. The 43 ICSRs contained a total of 61 AEs. There were 21 non-serious, medically confirmed AEs; 39 non-serious AEs, and 1 serious, non-medically confirmed AE. A summary tabulation of medication errors is available in Appendix 9.

Most ICSRs were non-serious (n=42, 97%). Of the total 61 AEs, the most frequently reported AEs were coded to PTs Vaccination error (n=13), Expired product administered (n=8), Product

administered to patient of inappropriate age (n=8) and Incomplete course of vaccination (n=5). AEs were reported alongside medication errors in a small percentage of cases, majority of which were non-serious events falling under different SOCs.

Of the 43 ICSRs, 17 were for females, 19 for males and 7 were of unknown gender; the age range was 9-80 years. The single serious report included the events of inappropriate schedule of vaccine and chest pain. The chest pain developed 2 days after receiving the primary dose and the event outcome was reported as recovering at the time of reporting. No further details were provided. Furthermore, only 9 out of 43 ICSRs were co-reported with AEs.

The reporting rate (rr) was 4.15 per 100,000 doses administered, equivalent to 0.00415% of all doses administered.

9.2.2 Conclusion

Overall, the reporting rate was very low. No trend was identified that would indicate a change from the established benefit-risk profile of NVX-CoV-2373. No new safety signal was identified.

10 NON-CLINICAL DATA

During the reporting interval, there were no safety findings from non-clinical studies that impacted the safety 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 administered on Days 0 and 21).

Table 10 provides summary of non-clinical studies either ongoing or completed during the reporting interval, for NVX-CoV2373.

Table 10: 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**
21#327 (Completed)	Swedish National Veterinary Institute (SVA) (in life) Novavax (Immunogenicity) Non-Good Laboratory Practices (Non-GLP)	BALB/c mice (10 mice/group, females)	SARS-CoV-2 rS, 1 µg ± Matrix-M, 5 µg SARS-CoV-2 rS 1 µg + Matrix-M (50% reduced aldehyde), 5 µg Administered SC on days 0 and 21 Immunogenicity evaluation anti-S IgG1 and IgG2a, hACE2 binding inhibition on Days 20 and 28.	No safety findings
22#335 (Completed)	SVA (in life) Novavax (immunogenicity) Non-GLP	BALB/c mice (10 mice/group, females)	SARS-CoV-2 rS, 0.3 µg SARS-CoV-2 rS, 0.3 µg + Matrix-M (ref) 10, 5, 2.5, 1.25 or 0.625 µg SARS-CoV-2 rS, 0.3 µg + Matrix-M (low purity) 10, 5, 2.5, 1.25 or 0.625 µg SARS-CoV-2 rS, 0.3 µg + Matrix-M (high particle size) 10, 5, 2.5, 1.25 or 0.625 µg Administered IM on days 0 and 14 Comparability evaluation: surrogate Virus Neutralisation Test on Days 13 and 20. Immunogenicity characterisation of anti-S IgG1 and IgG2a, CMI (Fluorospot IL-2, IFN-γ, IL-4) on Day 28	No safety findings

Table 10: 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)	UHSC (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 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)	5 µg Prototype BV2373 or Omicron BA.1 BV2515 + 50 µg Matrix-M1 Administered IM on Days 0 and 30	No safety findings

Table 10: 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 (Ongoing)	Texas Bio Med (in-life) Novavax (immunogenicity) Non-GLP	Rhesus Macaques (n = 5/group)	Day 0 and 21 Vaccination (IM) 5µg SARS-CoV-2 rS BV2373 + 5 µg Matrix-M1 5µg SARS-CoV-2 rS Delta + 5 µg Matrix-M1 6 Month Boost- 5 µg (2.5 µg if bivalent) SARS-CoV-2 rS + 50 µg Matrix-M1 Prototype (BV2373), Omicron BA.1 (BV2515) Placebo	No safety findings
702-158 Immunogenicity and Protective Efficacy of SARS-CoV-2 rS Omicron BA.1 in Mice (in-life Complete)	NLS (in-life) Novavax (immunogenicity) UMSOM (challenge) Non-GLP	BALB/c mice (n = 16/group)	0.1 and 1 µg SARS-CoV-2 rS BV2373 or Omicron BA.1 BV2509 + 5 µg Matrix-M1 All Administered IM as homologous or heterologous vaccines on Days 0 and 14 Challenge with Omicron BA.1 and N501.Y on Day 76	No safety findings
702-160 Immunogenicity of SARS-COV-2 rS Omicron BA.1 Variant BV02509 and BV2515 in Mice (in-life Complete)	NLS (in-life)	BALB/c mice (n = 10/group)	0.01, 0.1 and 1 mcg Prototype BV2373, Omicron BV2509 or BV2515 + 5mcg Matrix-M administered IM on days 0 and 14	No safety findings

11 LITERATURE

During the reporting interval and cumulatively, 4 literature articles were identified for discussion. Of these, 2 articles compared the immunogenicity of different COVID-19 vaccines (given either as homologous or heterologous regimens). The other 2 articles presented preliminary safety evaluation of NVX-CoV2373 based on reports from Health Authorities in Germany and South Korea, respectively.

Zhang et al published the results of humoral and cellular immune memory to four COVID-19 vaccines. This study compared humoral and cellular immune memory to four COVID-19 vaccines (including NVX-CoV2373) in a longitudinal fashion for individuals with no prior immunity, and provided a direct, side-by-side, comprehensive evaluation of effector and memory immune responses induced by different vaccine platforms. A study of blood samples from individuals who had participated in an investigational NVX-CoV2373 trial, where two intramuscular 5-µg doses of NVX-CoV2373 or placebo were administered 21 days apart was performed. The study revealed that at 6 months post immunisation, the neutralising antibody titres of NVX-CoV2373 were comparable to that of BNT162b2 and only moderately lower than mRNA-1273. NVX-CoV2373 elicited $CD4^+$ T cell memory and neutralising antibody titres comparable to the mRNA vaccines[1].

Stuart et al published the immunogenicity, safety, and reactogenicity results of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines study conducted in the UK (COM-COV2). This was a single-blind, randomised, phase 2 non-inferiority trial which studied the effects of mixed priming schedules incorporating an adenoviral-vectored vaccine (ChAdOx1 nCoV-19 [ChAd], AstraZeneca), two mRNA vaccines (BNT162b2 [BNT], Pfizer–BioNTech, and mRNA-1273 [m1273], Moderna) and NVX-CoV2373. Study details are included in Appendix 7 and Table 34. Adults aged 50 years and older, previously immunised with a single dose of ChAd or BNT in the community, were randomly assigned (in random blocks of three and six) within these cohorts in a 1:1:1 ratio to receive a second dose intramuscularly (8–12 weeks after the first dose) with the homologous vaccine, m1273, or NVX-CoV2373. The primary endpoint was the Geometric Mean Ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentrations measured by ELISA in heterologous versus homologous schedules at 28 days after the second dose, with a non-inferiority criterion of the GMR above 0·63 for the one-sided 98.75% CI. This trial only tested the boost of SARS-CoV-2 anti-spike IgG in recipients previously immunised with a single dose of ChAd or BNT in the community. The GMC 28 days after a boost of SARS-CoV-2 anti-spike IgG in recipients of was non-inferior to that of ChAd/ChAd recipients. BNT/NVX did not meet non-inferiority threshold when compared to homologous schedule of BNT/BNT. Findings from this trial demonstrated that the immunogenicity of heterologous booster with NVX following community prime with ChAd led to an immune response that may be superior when compared to homologous schedule and the T-cell response across all groups was greatest with ChAd/NVX, which might prove important in terms of durability of protection and protection against new SARS-CoV-2 variants. Together, these findings supported the use of mixed schedules[2].

Paul Ehrlich Institute (PEI) published an article that summarised the safety data for NVX-CoV2373 for the first 3 months since vaccination began in Germany. The preliminary evaluation of the vaccine indicated that the frequently reported adverse reactions were mostly non-serious and were previously well-studied in clinical trials. Two reports of anaphylaxis were adjudicated against a case definition and assessed as possible or probable cases of anaphylaxis. Anaphylaxis was noted as a rare side effect of other COVID-19 vaccines. Paraesthesia was reported relatively frequently post NUVAXOVID administration but was noted to also have been reported following the administration of other COVID-19 vaccines. No signal was identified for reports of myocarditis/pericarditis from Germany[3].

Hwang et al published an article based on monitoring of adverse events following initial vaccination with NUVAXOVID which was obtained from Korea Centres for Disease Control and Prevention (KCDC). The article summarises the safety data for NVX-CoV2373 from 14-Feb-2022 to 12-Mar-2022 in South Korea. The health status was evaluated by monitoring AEs reported through medical institutions, phone calls and text messages. A total of 123,786 people were vaccinated, and 240 AEs were reported, with a reporting rate of 193.9 per 100,000 cases. The majority of the reports were non-serious (95.4%). Most AEs occurred on the first and second day after vaccination, with the rate of symptoms gradually decreasing after that period, indicating a similar pattern as that observed with other vaccines. In patients cross-vaccinated with the NVX-CoV2373 (second and third doses), the most common symptoms were injection site pain, fatigue/lethargy, muscle pain, headache, and body ache. Reports of adverse events after the initial vaccination were somewhat lower than those reported with other COVID-19 vaccines and were also consistent with those reported by the EMA for NVX-CoV2373[4].

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 (monthly summary safety reports) submitted to relevant HA by SII (Covovax) and NVX (Nuvaxovid) are detailed in Table 11 below.

Table 11: Periodic SSRs Submitted to HA

SSR No.	Reporting Interval	Data Lock Point
Covovax SSR No. 05	01-Jan-2022 to 31-Jan-2022	31-Jan-2022
Nuvaxovid SSR No. 01	20-Dec-2021 to 28-Feb-2022	28-Feb-2022
Covovax SSR No. 06	01-Feb-2022 to 28-Feb-2022	28-Feb-2022
Nuvaxovid SSR No. 02	01-Mar-2022 to 31-Mar-2022	31-Mar-2022
Covovax SSR No. 07	01-Mar-2022 to 31-Mar-2022	31-Mar-2022
Nuvaxovid SSR No. 03	01-Apr-2022 to 30-Apr-2022	30-Apr-2022
Covovax SSR No. 08	01-Apr-2022 to 30-Apr-2022	30-Apr-2022
Nuvaxovid SSR No. 04	01-May-2022 to 31-May-2022	31-May-2022
Covovax SSR No. 09	01-May-2022 to 31-May-2022	30-Apr-2022

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Interim analysis data from 2019nCoV-301 and 2019nCoV302 studies concluded that both phase 3 pivotal studies have met primary efficacy endpoints for adults and adolescents. 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

14.1 Signals

On 27-Jun-2022, pursuant to PRAC request, the prespecified safety topics of “menstrual disorders” and “tachycardia and other rhythm abnormalities” became validated signals. Signal Evaluation Reviews (SER) were included in SSR No.06.

On 29-Jul-2022, pursuant to PMDA request, Acute Coronary syndrome (ACS) became a validated signal, and the SER will be provided in SSR No. 07.

A summary of new signals validated, after the data lock point are presented in Table 12.

14.2 Labelling Update

On 21-Jul-2022, CCDS V5.0 was released. Anaphylaxis has been added to Section 4.4 (Special Warnings and Precautions for Use), and both Anaphylaxis and Paraesthesia/Hypoaesthesia have been added to Section 4.8 (Undesirable side effects). The updated Company Core Safety Information (CCSI) was included with SSR No.06 (Data lock 31-Jul-2022).

On 03-Aug-2022, the AESI of myocarditis/pericarditis was reclassified from an important potential risk to an important identified risk. The CCDS and core RMP will be updated accordingly, and a Type 2 safety variation will be submitted to update the SmPC.

Table 12: Validated Signals Identified After the Data Lock Point

Signal Term	Date Detected	Status (New, Ongoing, or Closed)	Outcome (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
Menstrual disorders	27-Jun-2022	Closed	Refuted	N/A	PRAC Request (SSR No.04)	HA Request	Was included along with SSR No.06	Signal refuted based on current available data from clinical trials and post-marketing reports
Tachycardia and other Rhythm Abnormalities	27-Jun-2022	Closed	Refuted	N/A	PRAC Request (SSR No.04)	HA Request	Was included along with SSR No.06	Signal refuted based on current available data from clinical trials and post-marketing reports
Acute Coronary Syndrome (ACS)	29-Jul-2022	New	TBD	N/A	PMDA (SSR No.05)	HA Request	Ongoing	Pending

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

15.1 Validated Signals During the Reporting Interval

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

Following the DLP, SERs were completed for anaphylaxis, myocarditis/pericarditis, paraesthesia//hypoaesthesia, encephalitis/encephalomyelitis, chest pain/chest discomfort and dizziness for NVX-CoV2373. A summary of these topics as of 19-Jun-2022 are presented below. Complete evaluations are included in SERs in Appendix 20, Appendix 21, Appendix 22, Appendix 23, Appendix 24 and Appendix 25, respectively. Please note cut-off dates may vary from the interval summaries (19-Jun-2022 cut-off date) and SER documents.

Pursuant to HA inquiries received during the reporting interval, the prespecified AESI of encephalitis/encephalomyelitis and MedDRA PTs of Chest pain/Chest discomfort and Dizziness, became validated signals. These signals have been refuted based on lack of evidence supporting a causal association with NVX-CoV2373.

No signals were closed during the reporting interval.

15.1.1 Anaphylaxis

A signal of anaphylaxis was validated on 18-May-2022, following a request for a label update from TGA. The request was to update the Product Information section 4.4 (Special Warnings and Precautions for Use) and section 4.8 (Adverse Effects). The signal underwent evaluation and was confirmed as an identified risk post the cut-off date of this report. Refer to Section 14.2 for labelling updates. A complete signal evaluation was performed using the search strategy; MedDRA HLT: Anaphylactic and anaphylactoid responses, across cumulative data up to a cut-off date of 21-May-2022 and the SER is presented in (refer to Appendix 20). Of note, based on updates made to AESI master list, two different search strategies were employed in the database query used to identify cases reviewed for signal assessment in the SER versus those presented in this report.

For this report, a high specificity search of cumulative data was conducted with cut-off date of 19-Jul-2022 based on a narrow search strategy; MedDRA SMQ (Narrow): Anaphylactic reaction. Using this search strategy, O/E analyses were performed across cumulative data up to the cut-off date of the current reporting interval (19-Jun-2022) for pre-adjudicated cases meeting the risk-window inclusion criteria. O/E analyses were also run for the subset of medically confirmed ICSRs for a given AESI to refine results against those ICSRs reported by HCPs. The general methods of AESI analyses are presented in Section 15.2.1.

15.1.1.1 Results and Discussion

A total of 20 ICSRs were retrieved for the interval and cumulative period based on the narrow search strategy.

The 20 ICSRs included 20 AEs coded to PTs Anaphylactic reaction (n=15), Circulatory collapse (n=4), and Anaphylactic shock (n=1). All AEs were designated as serious by convention, meeting important medical event (IME) criteria, of which 2 AEs additionally involved hospitalisation, 1 AE met life threatening (LT) criteria, and 1 AE met other medically important condition criteria. Eleven out of 20 reports were non-medically confirmed.

Of the 20 ICSRs, 1 was for a male and 19 were for females; the age range was 25-55 years with a median age of 39 years. The majority of the ICSRs involved females, who fell in the age group of 35-55 years old (n=13/19, 68%). Almost half of the AEs reportedly occurred within 24 hours of vaccination (n=9, 45%).

Results of O/E with sensitivity analyses are presented in Table 14 and Table 15.

15.1.1.1.1 Results of O/E Analysis

The risk windows for anaphylaxis were 0-7, 0-1 and 0-2 days (refer to Table 36). The TTO for 15 of 20 AEs ranged from 0-3 days. The TTO was not reported for the other 5 AEs which were conservatively assessed as falling within all the risk windows. Therefore, all AEs (n=20) met inclusion criteria for the observed count for O/E analysis within risk window 0-7 days and 9 AEs (n=9) met inclusion criteria for the observed count for medically confirmed AEs within the same risk window. As 1 report fell outside of the risk windows of 0-2 days and 0-1 day, 19 of 20 AEs (n=19) met inclusion criteria for O/E analysis for these risk windows, and 8 of 9 medically confirmed AEs (n=8) met inclusion criteria for the observed count for medically confirmed AEs within these risk windows (refer to Table 13).

Table 13: Stratification of AEs Included in O/E Analysis

Total ICSRs		**n=20**	
Total AEs		**n=20**	
number of AEs with TTO reported		15	
number of AEs TTO missing (conservatively assessed as falling withing the risk window)		5	
AEs with TTO falling outside risk windows (All AEs)		**AEs with TTO falling outside risk windows (medically confirmed AEs)**	
Risk window 0-7 days	0	Risk window 0-7 days	0
Risk window 0-2 days	1	Risk window 0-2 days	1
Risk window 0-1 day	1	Risk window 0-1 day	1
Total AEs included in O/E analysis (all AEs) stratified by risk window		**Total AEs included in O/E analysis (medically confirmed AEs) stratified by risk window**	
Risk window 0-7 days	20	Risk window 0-7 days	9

Table 13: Stratification of AEs Included in O/E Analysis

Total ICSRs		**n=20**	
Total AEs		**n=20**	
number of AEs with TTO reported		15	
Risk window 0-2 days	19	Risk window 0-2 days	8
Risk window 0-1 day	19	Risk window 0-1 day	8

Risk window 0-7 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0-7 days (n=20, medically and non-medically confirmed), the observed rate was increased compared to the expected rate with a statistically significant RR of 16.07 (95% CI: 9.82 – 24.82).

When only medically confirmed anaphylaxis AEs were considered within a risk window of 0-7 days (n=9), observed rate was increased and statistically significant.

Risk window 0-2 days: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0-2 days (n=19, medically and non-medically confirmed), the observed rate was increased compared to the expected rate with a statistically significant RR of 62.86 (95% CI: 37.85 – 98.17).

When only medically confirmed anaphylaxis AEs were considered within a risk window of 0-2 days (n=8), observed rate was increased and statistically significant.

Risk window 0-1 day: When accounting for all cumulative anaphylaxis AEs meeting inclusion criteria within a risk window of 0-1 day (n=19, medically and non-medically confirmed), the observed rate was increased when compared to the expected rate with a statistically significant RR of 124.84 (95% CI: 75.16 – 194.94).

When only medically confirmed anaphylaxis AEs were considered within a risk window of 0-1 day (n=8), observed rate was increased and statistically significant.

Table 14: O/E Analysis of Anaphylaxis with Sensitivity Analysis for All Cumulative AEs

All Doses	**O/E Rate Ratio (95% CI)[a]**	**Assuming 50% Underreporting[b]**	**Assuming 75% Underreporting[b]**
All AEs			
Risk Window 0 – 7 Days	16.0703 (9.8189-24.8205)	32.1405 (19.6379-49.6411)	64.2811 (39.2757,99.2821)
Risk Window 0 – 2 Days	62.8633 (37.8503-98.1661)	125.7267 (75.7007-196.3321)	251.4534 (151.4014,392.6643)
Risk Window 0 – 1 Day	124.8350 (75.1638-194.9397)	249.6700 (150.3276-389.8794)	499.3400 (300.6552-779.7588)
Medically Confirmed AEs			
Risk Window 0 – 7 Days	7.2316 (3.3105-13.7240)	14.4632 (6.6210-27.4480)	28.9265 (13.2419-54.8961)

Table 14: O/E Analysis of Anaphylaxis with Sensitivity Analysis for All Cumulative AEs

All Doses	O/E Rate Ratio (95% CI)[a]	Assuming 50% Underreporting[b]	Assuming 75% Underreporting[b]
Risk Window 0 – 2 Days	26.4688 (11.4147-52.1435)	52.9375 (22.8293-104.2870)	105.8751 (45.6586-208.5739)
Risk Window 0 – 1 Day	52.5621 (22.6674-103.5473)	105.1242 (45.3348-207.0947)	210.2484 (90.6696-414.1894)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables.

[a] The CI is calculated using the method from Garwood 1936[5].

[b] Sensitivity analysis is used to adjust for underreporting. For the sensitivity assumption and calculation refer to Appendix 10.

15.1.1.1.1.1 Results of O/E Analysis Stratified by Age and Gender

The results of O/E analysis for anaphylaxis considering a 0-7-day risk window, stratified by age and gender, are presented in Table 15 below. When accounting for all cumulative anaphylaxis ICSRs (n=20) stratified by age and gender, the crude as reported rate in the total female group (n=19) showed an increase in the observed rate compared to the expected rate, and this increase was statistically significant with an RR of 27.72 (95% CI: 16.69 – 43.29). Similar results were noted in the 30-39-year-old female group (n=7) with an RR of 43.12 (95% CI 17.31 – 88.83) and in the 40-49-year-old female group (n=8) with an RR of 41.78 (95% CI 18.02 – 82.31).

When only medically confirmed reports were considered, in the total female group (n=9) the observed rate was increased when compared with the expected rate, and this increase was statistically significant with an RR of 13.13 (95% CI: 6.01 – 24.92). Similar results were noted in the 30-9-year-old female group (n=4) with an RR of 24.64 (95% CI: 6.71 – 63.08) and in the 40-49-year-old female group (n=3) with an RR of 15.67 (95% CI: 3.24 – 45.80).

Table 15: O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Gender

Age (in years)	Male		Female	
	Report Count	O/E Rate Ratio (95% CI)[a]	Report Count	O/E Rate Ratio (95% CI)[a]
All Reports				
0-19	0	0 (0-235.1710)	0	0 (0-1145.8684)
20-29	0	0 (0-128.7715)	1	12.5354 (0.3761-69.8221)
30-39	0	0 (0-74.1737)	7	43.1218 (17.3103-88.8310)
40-49	1	20.6672 (0.6200-115.1161)	8	41.7792 (18.0173-82.3050)
50-59	0	0 (0-82.8538)	1	6.3204 (0.1896-35.2046)
60-69	0	0 (0-170.8322)	1	14.7273 (0.4418-82.0313)
70-79	0	0 (0-422.8062)	0	0 (0-187.9395)
80+	0	0 (0-2213.9826)	0	0 (0-1293.1331)
Missing	0	N/A	1	N/A
Total	1	4.5660 (0.1370-25.4326)	19	27.7205 (16.6906-43.2877)

Table 15: O/E Analysis of Anaphylaxis for All Cumulative Reports Stratified by Age and Gender				
Age (in years)	**Male**		**Female**	
	Report Count	**O/E Rate Ratio (95% CI)[a]**	**Report Count**	**O/E Rate Ratio (95% CI)[a]**
All Reports				
Medically Confirmed Reports				
0-19	0	0 (0-235.1710)	0	0 (0-1145.8684)
20-29	0	0 (0-128.7715)	1	12.5354 (0.3761-69.8221)
30-39	0	0 (0-74.1737)	4	24.6411 (6.7147-63.0811)
40-49	0	0 (0-76.2618)	3	15.6672 (3.2379-45.8004)
50-59	0	0 (0-82.8538)	1	6.3204 (0.1896-35.2046)
60-69	0	0 (0-170.8322)	0	0 (0-54.3439)
70-79	0	0 (0-422.8062)	0	0 (0-187.9395)
80+	0	0 (0-2213.9826)	0	0 (0-1293.1331)
Missing	0	N/A	0	N/A
Total	0	0 (0-16.8485)	9	13.1307 (6.0110-24.9192)

15.1.1.1.2 Limitations of O/E Analysis Stratified by Age and Gender

Stratification by age and gender led to small absolute numbers for counts in many of the strata, increasing uncertainty and precluding ability to draw absolute conclusions The magnitude of the denominator was impacted by the very low person-time exposure; therefore, the RR was increased, even in a case of very low observed rate. Reflecting the low sample size, CIs are markedly widened which limits the interpretation of these results.

15.1.1.2 Conclusion

The O/E results showed a statistically significant increase in the observed count compared to the background rates. Similar result was seen in O/E analysis for all reports stratified by age and gender in the total female group, 30-39-year-old female group, and 40-49-year-old female group. When limited to medically confirmed reports, a statistically significant increase was seen in the same groupings.

As of 19-Jun-2022, the signal of anaphylaxis has been confirmed, and following cut-off date, CCDS 5.0 was released to include anaphylaxis in the current general warning and precautions section. The respective SER is presented in Appendix 20.

15.1.2 Myocarditis and Pericarditis

On 05-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 Food and Drug Administration

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 next monthly Summary Safety Report (SSR No.04 01-May-2022 to 31-May-2022).

A complete signal evaluation was performed using a broad search strategy across cumulative data up to cut-off date of 08-Jun-2022, and the SER is presented in Appendix 21. Upon evaluation of the SER and additional data requested by EMA PRAC after the data cut-off, as noted in the PRAC Assessment Report for SSR No.05 (01-Jun-2022 to 30-Jun-2022), the signal of myocarditis/pericarditis has been confirmed and related updates to product labelling have been initiated. The planned labelling updates are presented in Section 14.2.

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.

For the analyses in this report, a high specificity search of cumulative data was conducted with cut-off date of 19-Jul-2022 based on a narrow search strategy; MedDRA SMQ (narrow): Non-infectious myocarditis/pericarditis, HLTs: Non-infectious myocarditis; Non-infectious pericarditis. Using this search strategy, O/E analyses were performed across cumulative data up to the cut-off date of the current reporting interval (19-Jun-2022) for pre-adjudicated meeting hazard-window inclusion criteria. O/E estimates were performed for myocarditis (Section 15.1.2.1) and pericarditis (Section 15.1.2.2) separately, in addition to the combined conditions (Section 15.1.2.3). O/E analyses were also run for the subset of medically confirmed ICSRs for a given AESI to refine results against those ICSRs reported by HCPs. The methods of AESI analysis for the AESIs of myocarditis and pericarditis are presented in Section 15.2.1.

15.1.2.1 Myocarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using specific search strategy; MedDRA HLT: Non-infectious myocarditis

15.1.2.1.1 Results and Discussion

A total of 12 ICSRs were retrieved for the interval and cumulative period.

The 12 ICSRs included 12 AEs coded to PTs Myocarditis (n=8) and Myopericarditis (n=4). All 12 AEs were designated as serious by convention, meeting IME criteria, of which 5 AEs additionally involved hospitalisation. Nine out of 12 AEs were non-medically confirmed.

Of the 12 ICSRs, 7 were for females and 5 for males; the age range was 19-76 years with a median age of 32 years. The age range for 3/5 males and 6/7 females was between 19-47 years.

More than half of the ICSRs occurred in 19-39-year-old age group (n=7, 58%). TTO was rarely reported (n=5).

Results of O/E with sensitivity analyses are presented in Table 16. In addition, O/E was performed for cumulative AEs stratified by age and gender and is presented in Table 17.

15.1.2.1.1.1 Results of the O/E Analysis

The O/E analysis was performed for multiple risk windows for myocarditis. The risk windows for Myocarditis were 0-42 days, 0-30 days, 0-14 days, and 0-7 adys (refer to Table 36). The TTO for 5 of 12 AEs ranged from 0-4 days. The TTO was not reported for the other 7 AEs which were conservatively assessed as falling within all risk windows (0-42 days, 0-30 days, 0-14 days, and 0-7 days). Therefore, all AEs met inclusion criteria for the observed count (n=12) for O/E analysis within all risk windows and 3 AEs met inclusion criteria for the observed count (n=3) for O/E analysis for medically confirmed AEs within all risk windows.

Risk window 0-42 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0-42 days (n=12, medically and non-medically confirmed), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 8.55 (95% CI: 4.42 – 14.93).

When only medically confirmed myocarditis AEs were considered within a risk window of 0-42 days (n=3), results showed a statistically significant increase in the observed rate versus the expected rate, when assuming 75% underreporting, with an RR of 8.55 (95% CI:1.77 – 24.99).

Risk window 0-30 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0-30 days (n=12, medically and non-medically confirmed), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 10.00 (95% CI: 5.17 – 17.45).

When only medically confirmed myocarditis AEs were considered within a risk window of 30 days (n=3), there was a statistically significant increase in the observed versus the expected rate, when assuming 50% underreporting with an RR of 5.00 (95% CI: 1.03 – 14.62) and 75% underreporting with an RR of 10.00 (95% CI: 2.07 – 29.23).

Risk window 0-14 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0-14 days (n=12, medically and non-medically confirmed), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 17.22 (95% CI: 8.90 – 30.08).

When only medically confirmed AEs were considered within a risk window of 0-14 days (n=3), there was a statistically significant increase in the observed rate versus the expected rate when assuming 50% underreporting and 75% underreporting.

Risk window 0-7 days: When accounting for all cumulative myocarditis AEs meeting inclusion criteria within a risk window of 0-7 days (n=12, medically and non-medically confirmed), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 34.12 (95% CI: 17.63 – 59.60).

When only medically confirmed AEs were considered within a risk window of 0-7 days (n=3), the crude observed rate as reported, showed a statistically significant increase when compared to the expected rate with an RR of 8.53 (95% CI: 1.76 – 24.94).

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

All Doses	O/E Rate Ratio (95% CI)[a]	Assuming 50% Underreporting[b]	Assuming 75% Underreporting[b]
All AEs			
Risk Window 0-42 Days	8.5479 (4.4164-14.9304)	17.0958 (8.8328-29.8607)	34.1917 (17.6657-59.7214)
Risk Window 0-30 Days	9.9997 (5.1665-17.4661)	19.9994 (10.3330-34.9323)	39.9988 (20.6660-69.8645)
Risk Window 0-14 Days	17.2217 (8.8979-30.0806)	34.4434 (17.7958-60.1611)	68.8868 (35.5915-120.3222)
Risk Window 0-7 Days	34.1245 (17.6310-59.6041)	68.2489 (35.2619-119.2081)	136.4979 (70.5239-238.4163)
Medically Confirmed AEs			
Risk Window 0-42 Days	2.1370 (0.4416-6.2471)	4.2740 (0.8833-12.4942)	8.5479 (1.7666-24.9884)
Risk Window 0-30 Days	2.4999 (0.5167-7.3081)	4.9998 (1.0333-14.6162)	9.9997 (2.0666-29.2324)
Risk Window 0-14 Days	4.3054 (0.8898-12.5862)	8.6108 (1.7796-25.1724)	17.2217 (3.5592-50.3448)
Risk Window 0-7 Days	8.5311 (1.7631-24.9393)	17.0622 (3.5262-49.8786)	34.1245 (7.0524-99.7572)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables

[a] The CI is calculated using the method from Garwood 1936[1].

[b] Sensitivity analysis is used to adjust for underreporting. For the sensitivity assumption and calculation refer to Appendix 10.

15.1.2.1.1.1.1 Results of O/E Analysis Stratified by Age and Gender

The results of O/E analysis for myocarditis considering a 0-42-day risk window, stratified by age and gender, are presented in Table 17 below. When accounting for all cumulative myocarditis AEs (n=12), stratified by age and gender, the crude observed rate as reported in the total male group (n=5, medically and non-medically confirmed) showed a statistically significant increase in the observed rate compared to the expected rate with an RR of 8.38 (95% CI: 2.72 – 19.569).

Similar results were reported in the total female group (n=7) with an RR 12.39 (95% CI: 4.97 – 25.53). This was also the case for the 0-19-year-old male group (n=1) with an RR of 111.76 (95% CI: 3.35 – 622.51) and the 20-29-year-old female group (n=4) with an RR of 77.96 (95% CI: 21.24 – 199.58). No stratified O/E results were statistically significant when considering only medically confirmed myocarditis AEs (n=3).

Table 17: O/E Analysis of Myocarditis for All Cumulative Reports Stratified by Age and Gender

	Male		Female	
Age (in years)	**Report Count**	**O/E Rate Ratio (95% CI)[a]**	**Report Count**	**O/E Rate Ratio (95% CI)[a]**
All Reports				
0-19	1	111.7618 (3.3529 - 622.5134)	0	0 (0 - 4293.5483)
20-29	0	0 (0 - 30.3835)	4	77.9609 (21.2443 - 199.5799)
30-39	1	5.1684 (0.1551 - 28.7879)	1	7.9566 (0.2387 - 44.3182)
40-49	1	7.6261 (0.2288 - 42.4776)	1	7.3132 (0.2194 - 40.7346)
50-59	1	12.8856 (0.3866 - 71.7727)	0	0 (0 - 28.7970)
60-69	1	26.7056 (0.8012 - 148.7501)	0	0 (0 - 44.9951)
70-79	0	0 (0 - 185.6081)	1	31.0677 (0.9320 - 173.0469)
80+	0	0 (0 - 547.4130)	0	0 (0 - 462.7936)
Missing	0	N/A	0	N/A
Total	5	8.3797 (2.7150 - 19.5582)	7	12.3916 (4.9744 - 25.5268)
Medically Confirmed Reports				
0-19	0	0 (0 - 412.4012)	0	0 (0 - 4293.5483)
20-29	0	0 (0 -30.3835)	1	19.4902 (0.5847 - 108.5605)
30-39	0	0 (0 - 19.0714)	0	0 (0 - 9.3598)
40-49	1	7.6261 (0.2288 - 42.4776)	0	0 (0 - 26.9858)
50-59	0	0 (0 - 47.5478)	0	0 (0 - 28.7970)
60-69	1	26.7056 (0.8012 - 148.7501)	0	0 (0 - 44.9951)
70-79	0	0 (0 - 185.6081)	0	0 (0 - 114.6397)
80+	0	0 (0 - 547.4130)	0	0 (0 - 462.7936)
Missing	0	N/A	0	N/A
Total	2	3.3519 (0.4022 - 12.1003)	1	1.7702 (0.0531 - 9.8602)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables.

[a] The CI is calculated using the method from Garwood 1936[1].

15.1.2.1.2 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2.1, the possibility of overestimation of the observed count for myocarditis must be considered, as 7 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator.

15.1.2.1.2.1 Limitations to O/E Analysis Stratified by Age and Gender

Stratification by age and gender led to small absolute numbers for counts in many of strata, increasing uncertainty and precluding ability to draw absolute conclusions. The magnitude of the denominator is impacted by the very low person-time exposure; therefore, the RR is increased, even in a case of very low observed rate. CIs are markedly widened which limits the interpretation of these results. Additionally, caution should be taken when interpreting the marked increase in observed count compared to expected count for males 0-19 years old, as NVX-CoV2373 was not authorised for patients under 18 years of age in all regions, leaving limited number of doses received, making it more susceptible to extreme results.

15.1.2.1.3 Conclusion

The O/E result showed an increased observed rate that was statistically significant. When limited to medically confirmed AEs, the increase was not statistically significant. In addition, all risk windows present a statistically significant increase when considering all AEs. For the medically confirmed cases, only the risk window of 0-7 days presented a statistically significant increase.

The O/E result for all reports stratified by age and gender showed a statistically significant increase in the total male and female groups, 0-19-year-old male group, 20-29-year-old female group, and 40–49-year-old female group.

Based on review of myocarditis reports pooled with pericarditis, this AESI was identified as a signal and underwent signal evaluation, and the SER is presented in Appendix 21.

15.1.2.2 Pericarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Non-infectious pericarditis.

15.1.2.2.1 Results and Discussion

A total of 32 ICSRs were retrieved for the interval and cumulative period.

The 32 ICSRs included 32 AEs coded to PTs Pericarditis (n=32). All 32 AEs were designated as serious by convention, meeting IME criteria, of which 10 AEs additionally involved hospitalisation. Nineteen out of 32 AEs were non-medically confirmed.

Of the 32 ICSRs, 21 were for males and 11 for females; the age range was 19-65 years with a median age of 40 years. The age range for 18/21 males and 9/11 females was between 19-48 years. Majority of the ICSRs occurred in 19-40-year-old age group (n=19, 59%).

Results of O/E with sensitivity analyses are presented in Table 18. In addition, O/E was performed for cumulative AEs stratified by age and gender and is presented in Table 19.

15.1.2.2.1.1 Results of the O/E Analysis

The risk window identified for pericarditis was 0 to 42 days (refer to Table 36). The TTO for 22 of 32 AEs ranged from 0 to 23 days. TTO was not reported in the other 10 AEs which were conservatively assessed as falling within the risk window. All AEs met inclusion criteria for the observed count (n=32) for O/E analysis. Thirteen of 32 AEs met inclusion criteria for the O/E analysis for medically confirmed AEs (n=13).

When accounting for all cumulative pericarditis AEs meeting inclusion criteria (n=32, medically and non-medically confirmed), the observed rate showed an increase compared to the expected rate with a statistically significant RR of 4.59 (95% CI: 3.14 – 6.48).

When only medically confirmed AEs were considered (n=13), the crude observed rate as reported showed a not statistically significant increase compared to the expected rate. When assuming 50% underreporting and 75% underreporting the observed rate was increased when compared to the expected rate, and this increase was statistically significant.

Table 18: O/E Analysis of Pericarditis with Sensitivity Analysis for All Cumulative AEs

All Doses	O/E Rate Ratio (95% CI)[a]	Assuming 50% Underreporting[b]	Assuming 75% Underreporting[b]
All AEs			
All	4.5913 (3.1407-6.4809)	9.1825 (6.2814-12.9617)	18.3651 (12.5629-25.9234)
Medically Confirmed AEs			
Risk Window 0-42 Days	1.8652 (0.9929-3.1895)	3.7304 (1.9857-6.3790)	7.4608 (3.9714-12.7580)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables

[a] The CI is calculated using the method from Garwood 1936[1].

[b] Sensitivity analysis is used to adjust for underreporting. For the sensitivity assumption and calculation refer to Appendix 10.

15.1.2.2.1.1.1 Results of O/E Analysis Stratified by Age and Gender

The results of O/E analysis for pericarditis considering a 0-42-day risk window, stratified by age and gender, are presented in Table 19 below. When accounting for all cumulative pericarditis AESI reports (n=32), stratified by age and gender, the crude as reported observed rate in the total male group (n=21, medically and non-medically confirmed) showed an increase when compared to the expected rate and this was statistically significant with an RR 6.71 (95% CI: 4.15 – 10.26). Similar results were noted in the 0-19-year-old male group (n=1) with an RR of 60.88 (95% CI: 1.83 -339.13), the 20-39-year-old male group (n=12) with an RR of 10.18 (95% CI: 5.26 – 17.78) and the 40-59-year-old male age group (n=7) with an RR 5.35 (95% CI: 2.15 – 11.02). The crude as reported observed rate in the total female group (n=11, medically and non-medically confirmed) showed an increase when compared to the expected rate and this was statistically significant with an RR of 3.32 (95% CI: 1.66 – 5.94). Similar results were noted in the 20-39-year-old female group (n=5) with an RR of 5.60 (95% CI: 1.82 – 13.08).

When only medically confirmed reports of pericarditis were considered, the observed rate was increased when compared with the expected rate in the total male group (n=10), and this increase was statistically significant with an RR of 3.19 (95% CI: 1.53 – 5.88). Similar results were noted in the 20-39-year-old male group (n=6) with an RR of 5.09 (95% CI: 1.87 – 11.08).

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

	Male		Female	
Age (in years)	**Report Count**	**O/E Rate Ratio (95% CI)[a]**	**Report Count**	**O/E Rate Ratio (95% CI)[a]**
All Reports				
0-19	1	60.8846 (1.8265 - 339.1272)	0	0 (0 - 732.0307)
20-39	12	10.1783 (5.2588 - 17.7782)	5	5.6042 (1.8157 - 13.0801)
40-59	7	5.3488 (2.1472 - 11.0185)	4	2.9582 (0.8061 - 7.5730)
60+	0	0 (0- 9.0124)	2	3.1628 (0.3795 - 11.4178)
Missing	1	N/A	0	N/A
Total	21	6.7092 (4.1533 - 10.2555)	11	3.3213 (1.6577 - 5.9422)
Medically Confirmed Reports				
0-19	0	0 (0 - 224.6641)	0	0 (0 - 732.0307)
20-39	6	5.0892 (1.8660 - 11.0774)	1	1.1208 (0.0336 - 6.2430)
40-59	4	3.0564 (0.8329 - 7.8245)	1	0.7396 (0.0222 - 4.1193)
60+	0	0 (0 - 9.0124)	1	1.5814 (0.0474 - 8.8085)
Missing	0	N/A	0	N/A
Total	10	3.1949 (1.5335 - 5.8754)	3	0.9058 (0.1872 - 2.6480)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables

[a] The CI is calculated using the method from Garwood 1936[1].

15.1.2.2.2 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2.1, the possibility of overestimation of the observed count for pericarditis must be considered, as 10 AEs with unknown TTO were conservatively assessed as falling within the risk window and included in the observed count, potentially inflating the numerator.

15.1.2.2.2.1 Limitations to O/E Analysis Stratified by Age and Gender

Stratification by age and gender led to small absolute numbers for counts in many of strata, increasing uncertainty and precluding ability to draw absolute conclusions. The magnitude of the denominator is impacted by the very low person-time exposure; therefore, the RR is increased, even in a case of very low observed rate. CIs are markedly widened which limits the interpretation of these results. Additionally, caution should be taken when interpreting the marked increase in observed count compared to expected count for males 0-19 years old, as

NVX-CoV2373 was not authorised for patients under 18 years of age in all regions, leaving limited number of doses received, making it more susceptible to extreme results.

15.1.2.2.3 Conclusion

The O/E results showed a statistically significant increase in the observed count compared to the background rates except for the medically confirmed AEs for which results were not statistically significant.

The O/E result for all reports stratified by age and gender showed a statistically significant increase in the total male and total female groups, 0-19-year-old male group, 20-39-year-old male group, and 40-59-year-old male group. When limited to medically confirmed reports, a statistically significant increase was seen in the total male group and 20-39-year-old male group.

Based on review of pericarditis reports pooled with myocarditis, this AESI was identified as a signal and underwent signal evaluation, and the SER is presented in Appendix 21.

15.1.2.3 Myocarditis, Pericarditis

The global vaccine safety database was queried for interval and cumulative ICSRs using MedDRA SMQ (narrow): Non-infectious myocarditis/pericarditis, HLTs: Non-infectious myocarditis; Non-infectious pericarditis.

15.1.2.3.1 Results and Discussion

A total of 44 ICSRs were retrieved for the interval and cumulative period using the narrow search strategy.

The 44 ICSRs retrieved for the AESI of myocarditis and pericarditis included a total of 46 AEs coded to PTs Pericarditis (n=32), Myocarditis (n=8), Myopericarditis (n=4) and Carditis (n=2). All 46 AEs were designated as serious by convention, meeting IME criteria, of which 15 AEs additionally involved hospitalisation. Thirty out of 46 AEs were non-medically confirmed.

Of the 44 ICSRs, 25 were for males and 19 for females; the age range was 19-76 years with a median of 40. The age range of 20/25 males and 16/19 females was between 19-48 years. The majority of the ICSRs were for 19–29-year-old age group (n=16, 36.3%). In almost half of the reports, the TTO ranged from 0-5 days (n=21, 48%). Individually, for myocarditis (including myopericarditis), there were 7/12 (58%) ICSRs involving females. The age of 6/7 (85.7%) females and 3/5 (60%) males ranged between 19-47 years. Individually, for pericarditis, there were 21/32 (67%) ICSRs involving males. The age of 18/21 (86%) males and 9/11 (82%) females ranged between 19-48 years.

Results of O/E with sensitivity analyses are presented in Table 21. In addition, O/E was performed for cumulative AEs stratified by age and gender and is presented in Table 22.

15.1.2.3.1.1 Results of the O/E Analysis

The O/E analysis was performed for multiple risk windows for myocarditis, pericarditis. The risk windows were 0-42 days, 0-30 days, 0-14 days, and 0-7 days (refer to Table 36). The TTO for 28 of 46 AEs ranged from 0 to 23 days. The TTO was not reported for the other 18 AEs which were conservatively assessed as falling within the risk window 0-42 days. Additionally, one of the reports contained 2 AEs coded to PTs of Myopericarditis and Pericarditis which reportedly occurred on the same day and hence were pooled in one report for the O/E analysis. Therefore, after pooling two AEs into one report, 45 of 46 AEs (n=45) met inclusion criteria for the observed count for O/E analysis within risk window 0-42 days and 0-30 days and 16 AEs (n=16) met inclusion criteria for the medically confirmed AEs within the same risk windows. Since one AE fell outside of the risk window of 0-14 days, 44 of 45 AEs met inclusion criteria for the observed count (n=44) for O/E analysis of all AEs and 15 AEs met inclusion criteria for the observed count (n=15) for medically confirmed AEs within this risk window. Five AEs fell outside of the risk window of 0-7 days, hence 40 of 45 AEs met inclusion criteria for the observed count (n=40) for O/E analysis of all AEs within this risk window, and 11 AEs met inclusion criteria for the observed count (n=11) for O/E analysis for medically confirmed AEs within the same risk window (refer to Table 20).

Table 20: Stratification of AEs Included In O/E Analysis for Myocarditis and Pericarditis

Total ICSRs		**n=44**	
Total AEs		**n=45**	
number of AEs with TTO reported		27	
number of AEs TTO missing (conservatively assessed as falling withing the risk window)		18	
AEs with TTO falling outside risk windows (All AEs)		**AEs with TTO falling outside risk windows (medically confirmed AEs)**	
Risk window 0-42 days	0	Risk window 0-42 days	0
Risk window 0-30 days	0	Risk window 0-30 days	0
Risk window 0-14 day	1	Risk window 0-14 day	1
Risk window 0-7 days	5	Risk window 0-7 days	5
Total AEs included in O/E analysis (all AEs) stratified by risk window		**Total AEs included in O/E analysis (medically confirmed AEs) stratified by risk window**	
Risk window 0-42 days	45	Risk window 0-42 days	16
Risk window 0-30 days	45	Risk window 0-30 days	16
Risk window 0-14 day	44	Risk window 0-14 day	15
Risk window 0-7 days	40	Risk window 0-7 days	11

Risk window 0-42 days: When accounting for all cumulative myocarditis, pericarditis AESI reports meeting inclusion criteria within a risk window of 0-42 days (n=45, medically and non-medically confirmed), the observed rate showed an increase when compared to the expected rate with a statistically significant RR of 6.74 (95% CI: 4.92 – 9.02).

When only medically confirmed AEs were considered within a risk window of 0-42 days (n=16), all observed rates were increased and statistically significant.

Risk window 0-30 days: When accounting for all cumulative myocarditis, pericarditis AESI reports meeting inclusion criteria within a risk window of 0-30 days (n=45, medically and non-medically confirmed), observed rate showed an increase when compared to the expected rate with a statistically significant RR of 7.95 (95% CI: 5.80 – 10.64).

When only medically confirmed AEs were considered within a risk window of 0-30 days (n=16), all observed rates were increased and statistically significant.

Risk window 0-14 days: When accounting for all cumulative myocarditis, pericarditis AESI reports meeting inclusion criteria within a risk window of 0-14 days (n=44, medically and non-medically confirmed), the crude observed rate as reported, showed an increase when compared to the expected rate with a statistically significant RR of 13.40 (95% CI: 9.73 – 17.98).

When only medically confirmed AEs were considered within a risk window of 14 days (n=15), all observed rates were increased and statistically significant.

Risk window 0-7 days: When accounting for all cumulative myocarditis, pericarditis AESI reports meeting inclusion criteria within a risk window of 0-7 days (n=40, medically and non-medically confirmed), the observed rate as reported, showed an increase when compared to the expected rate with a statistically significant RR of 24.13 (95% CI: 17.24 – 32.86).

When only medically confirmed AEs were considered within a risk window of 7 days (n=11), all observed rates were increased and statistically significant.

Table 21: O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

All Doses	O/E Rate Ratio (95% CI)[a]	Assuming 50% Underreporting[b]	Assuming 75% Underreporting[b]
All AEs			
Risk Window 0-42 Days	6.7395 (4.9153-9.0174)	13.4789 (9.8306-18.0348)	26.9579 (19.6613-36.0696)
Risk Window 0-30 Days	7.9545 (5.8015-10.6431)	15.9090 (11.6029-21.2862)	31.8179 (23.2059-42.5724)
Risk Window 0-14 Days	13.3950 (9.7327-17.9827)	26.7899 (19.4653-35.9655)	53.5798 (38.9306-71.9309)
Risk Window 0-7 Days	24.1290 (17.2401-32.8576)	48.2579 (34.4803-65.7152)	96.5158 (68.9606-131.4304)
Medically Confirmed AEs			
Risk Window 0-42 Days	2.3963 (1.3704-3.8909)	4.7925 (2.7407-7.7818)	9.5850 (5.4814-15.5637)
Risk Window	2.8283 (1.6174-4.5924)	5.6565 (3.2348-9.1848)	11.3130 (6.4696-18.3695)

Table 21: O/E Analysis of Myocarditis, Pericarditis with Sensitivity Analysis for All Cumulative AEs

All Doses	O/E Rate Ratio (95% CI)[a]	Assuming 50% Underreporting[b]	Assuming 75% Underreporting[b]
All AEs			
0-30 Days			
Risk Window 0-14 Days	4.5665 (2.5572-7.5316)	9.1329 (5.1144-15.0632)	18.2658 (10.2289-30.1265)
Risk Window 0-7 Days	6.6355 (3.3117-11.8714)	13.2709 (6.6234-23.7429)	26.5419 (13.2468-47.4858)

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document, refer to **Appendix 10**.

Note: Refer to **Appendix 11** and **Appendix 12** for complete view of O/E tables

a The CI is calculated using the method from Garwood 1936**1**.

b Sensitivity analysis is used to adjust for underreporting. For the sensitivity assumption and calculation refer to **Appendix 10**.

15.1.2.3.1.1.1 Results of O/E Analysis Stratified by Age and Gender

When accounting for all cumulative myocarditis, pericarditis AESI reports with a risk window of 0-42 days (n=45, medically and non-medically confirmed), stratified by age and gender, the crude as reported observed rate in the total male group (n=25, medically and non-medically confirmed), was increased when compared with the expected rate, and this increase was statistically significant with an RR of 9.80 (95% CI: 6.35 – 14.48). Similar results were noted in the 20-29-year old male group (n=9) with an RR of 21.52 (95% CI: 9.85 – 40.83), the 30-39-year-old male group (n=4) with an RR of 5.45 (95% CI: 1.49 – 13.96), the 40-49-year-old male group (n=6) with an RR of 11.64 (95% CI: 4.27 – 25.34), and the 50-59-year-old male group (n=3) with an RR 6.41 (95% CI: 1.33 – 18.75). The crude as reported observed rate in total female group (n=20, medically and non-medically confirmed), was increased when compared with the expected rate, and this increase was statistically significant with an RR of 7.32 (95% CI: 4.47 – 11.31). Similar results were noted in the 20-29-year-old female group (n=7) with an RR of 32.95 (95% CI: 13.23 – 67.88), the 30-39-year-old female group (n=4) with an RR of 8.21 (95% CI: 2.24 – 21.01) and the 40-49-year-old female group (n=6) with an RR of 9.20 (95% CI: 3.37 – 20.01).

When only medically confirmed reports were considered, the crude as reported observed rate in the total male group (n=12) was increased when compared with the expected rate, and this increase was statistically significant with an RR of 4.71 (95% CI: 2.43 – 8.22). Similar results were noted in the 20-29-year-old male group (n=3) with an RR 7.17 (95% CI: 1.48 – 20.97) and the 40-49-year-old male group (n=3) with an RR of 5.82 (95% CI: 1.20 – 17.01).

Table 22: O/E Analysis of Myocarditis and Pericarditis for All Cumulative Reports Stratified by Age and Gender

	Male		Female	
Age (in years)	**AE Count**	**O/E Rate Ratio (95% CI)[a]**	**AE Count**	**O/E Rate Ratio (95% CI)[a]**
All AEs				
0-19	1	32.8532 (0.9856-182.9923)	0	0 (0-1443.7384)
20-29	9	21.5167 (9.8499-40.8339)	7	32.9538 (13.2286-67.8849)
30-39	4	5.4534 (1.4860-13.9606)	4	8.2081 (2.2367-21.0128)
40-49	6	11.6399 (4.2680-25.3362)	6	9.1950 (3.3715-20.0145)
50-59	3	6.4149 (1.3257-18.7529)	0	0 (0-4.9530)
60-69	1	4.4922 (0.1348-25.0216)	2	4.8271 (0.5793-17.4258)
70-79	0	0 (0-29.8177)	1	5.5328 (0.1660-30.8174)
80+	0	0 (0-96.8406)	0	0 (0-102.1187)
Missing	1	N/A	0	N/A
Total	25	9.8047 (6.3456-14.4717)	20	7.3232 (4.4745-11.3108)
Medically Confirmed AEs				
0-19	0	0 (0- 121.2283)	0	0 (0-1443.7384)
20-29	3	7.1722 (1.4823-20.9668)	1	4.7077 (0.1412-26.2218)
30-39	3	4.0900 (0.8453-11.9565)	1	2.0520 (0.0616-11.4298)
40-49	3	5.8199 (1.2028-17.0137)	1	1.5325 (0.0460-8.5360)
50-59	2	4.2766 (0.5132-15.4385)	0	0 (0-4.9530)
60-69	1	4.4922 (0.1348-25.0216)	1	2.4135 (0.0724-13.4434)
70-79	0	0 (0-29.8177)	0	0 (0-20.4159)
80+	0	0 (0-96.8406)	0	0 (0-102.1187)
Missing	0	N/A	0	N/A
Total	12	4.7062 (2.4316-8.2202)	4	1.4646 (0.3991-3.7495)

Abbreviations: Refer to List of Abbreviations.

Note: Sources of risk window, background IR, and administration data are presented in the accompanying O/E assumptions document,

refer to Appendix 10.

Note: Refer to Appendix 11 and Appendix 12 for complete view of O/E tables

[a] The CI is calculated using the method from Garwood 1936[1].

15.1.2.3.2 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2.1, the following limitations specific to combined myocarditis and pericarditis should be considered when interpreting the results of the O/E and sensitivity analyses. One ICSR with 2 events corresponding to a single clinical occurrence of Myopericarditis was identified and counted as 2 separate events observed count, falsely inflating the numerator in O/E and sensitivity analyses for combined Myocarditis and Pericarditis. Overestimation of the observed count for myocarditis/pericarditis should be considered, as 18 AEs lacking TTO were conservatively

assessed as falling within the risk window for the purpose of O/E analysis, thus observed counts may be artificially elevated in O/E analysis.

15.1.2.3.2.1 Limitations to O/E Analysis Stratified by Age and Gender

Stratification by age and gender led to small absolute numbers for counts in many of the strata, increasing uncertainty and precluding ability to draw conclusions. The magnitude of the denominator was impacted by the very low person-time exposure, therefore, the RR was increased, even in a case of very low observed rate. Additionally, caution should be taken when interpreting the marked increase in observed count compared to expected rate for 0-19-year-old male group, as NVX-CoV2373 is not authorised for individuals under 18 years of age in most countries, leaving theoretically only a narrow age group of 18-19-year-old males with limited number of doses received, making it more susceptible to extreme results. In addition, background rate used to compare the observed to the expected results included 0-19 years old. CIs are markedly wide which limits the interpretation of these results

15.1.2.3.3 Conclusion

The O/E results for cumulative myocarditis and pericarditis showed a statistically significant increase in the observed events compared to the background rates even when considering only medically confirmed cases.

The O/E result for all reports stratified by age and gender showed a statistically significant increase in the total male and total female groups, 20-29-year-old male and female groups, 30-39-year-old male and female groups, 40-49-year-old male and female groups, and the 50-59-year-old male group. When limited to medically confirmed AEs, the increase was not statistically significant except in the total male group, 20-29-year-old male group, and 40-49-year-old male group.

This AESI underwent signal evaluation and the SER is presented in Appendix 21. Following the cut-off date of 19-Jun-2022, myocarditis/pericarditis was confirmed as an important identified risk. The planned labelling updates are presented in Section 14.2.

15.1.3 Paraesthesia

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 (Adverse Effects) to include paraesthesia/hypoaesthesia. The NVX Safety Review Team confirmed this signal as a new identified risk. A complete signal evaluation was performed broad search strategy across cumulative data up to a cut-off date of 31-May-2022 based on MedDRA HLT: Paraesthesias and dysaesthesias and the SER is presented in Appendix 22.

15.1.3.1 Results and Discussion

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Paraesthesias and dysaesthesias with a cut-off date of 19-Jun-2022.

During the reporting interval and cumulatively, the database identified 252 ICSRs meeting the prespecified search strategy for paraesthesia. The 252 ICSRs contained a total of 314 AEs including 10 serious and 17 non-serious medically confirmed AEs; 28 serious and 259 non-serious, non-medically confirmed AEs. Of the total 314 AEs reported, the most frequently reported PTs included Hypoaesthesia (n=69), Paraesthesia (n=205) and Burning sensation (n=25). Of the 252 ICSRs, 197 were for females (78.2%) and 55 (21.8%) for males; the age range was 19-81 years with a median age of 45 year. Where time to onset was reported, most events occurred within the first week following vaccination. (n=121). The majority of AEs were non-serious, non-medically confirmed (n=259, 82.4%). The ICSRs were predominantly reported in the age group of 30-70 years (199, 79%). The outcome of majority of events was reported as not recovered, and 2 reports indicated event outcome of resolved with sequelae. It is early in the post-marketing experience with NVX-CoV2373 (no reports were received before 21-Feb-2022) and it is therefore difficult to draw conclusions with the current data; however, long-term sequelae are unlikely.

Based on the review of the reported ICSRs, paraesthesia was generally described one of two clinical scenarios: either paraesthesia as a subset of generalised symptoms consistent with systemic reactogenicity, or paraesthesia associated with localised neuromotor symptoms. Associated generalised symptoms included headache, fever, rash, pain (including abdominal pain), nausea, vomiting, diarrhoea, fatigue, dizziness, brain fog, chest pain, and palpitations. Reports describing paraesthesia alone or in association with neurologic or motor symptoms included lymphadenopathy, rash, pain or swelling limited to the affected limbs. Two reports of facial nerve palsy were associated with paraesthesia and/or hypoesthesia, though one report indicated that the patient also had a possible shingles outbreak. No pattern was evident to suggest paraesthesia as a sign or symptom of progressive polyneuropathy.

The rr was 24.37 per 100,000 doses administered, equivalent to 0.02437% of all doses administered.

15.1.3.2 Conclusion

The signal of paraesthesia /hypoaesthesia has been confirmed, and following cut-off date, the CCDS has been updated to include paraesthesia/hypoaesthesia under undesirable effects. The labelling updates are presented in Section 14.2.

15.1.4 Encephalitis and Encephalomyelitis

Pursuant to South Korea Health Authority communication, encephalitis, encephalomyelitis became a validated signal on 15-Jun-2022 and underwent signal evaluation, based on which this signal was refuted. A complete signal evaluation was performed using a broad search strategy

(MedDRA HLTs: Encephalitis nonviral infectious; Encephalitis of viral origin; Encephalitis NEC, and MedDRA SMQ (broad): Non-infectious encephalitis) across cumulative data up to a cut-off date of 30-Jun-2022 and the SER is presented in Appendix 23. The most comprehensive data capture is provided in the SER, due to extended cut-off period for the comprehensive review.

For this report, a high specificity search of cumulative data was conducted with cut-off date of 19-Jul-2022 based on a narrow search strategy; MedDRA SMQ (narrow): Non-infectious encephalitis. Using this search strategy, O/E analyses were performed across cumulative data up to the cut-off date of the current reporting interval (19-Jun-2022) for pre-adjudicated cases meeting the risk-window inclusion criteria. The general methods of AESI analyses are presented in Section 15.2.1.

15.1.4.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period using the narrow search strategy. The single ICSR included 1 AE coded to PT Non-infective encephalitis (n=1). This AE was designated as serious by convention, meeting IME criteria, and was non-medically confirmed.

This report concerned a 42-year-old female who experienced non-infective encephalitis (unknown TTO) with co-reported events of confusional state, diarrhoea, migraine, muscle twitching and pyrexia. The event outcome of non-infective encephalitis was reported as unknown. The single report of encephalitis did not contain information regarding the clinical status of the patient, physical examination findings or diagnostic workup, thus the case is considered Level 4 BC[6] criteria for encephalitis.

The methods of AESI analysis are presented in Section 15.2.1 and results of O/E analyses are presented below.

15.1.4.2 Results of the O/E Analysis

TTO was not provided in the single AE and was conservatively assumed to fall within the risk window 0-42 days (refer to Table 36). O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.1.4.3 Conclusions

The single report of encephalitis is considered Level 4 BC criteria for encephalitis due to insufficient information. This single ICSR met the TTO inclusion criteria and results of O/E analyses showed lower than expected background rates. A comprehensive review of this signal based on broad search strategy is presented in its respective SER in Appendix 23.

15.1.5 Chest Pain/Chest Discomfort

A signal of chest pain was validated on 15-Jun-2022 after a request was received from Health Canada pursuant in their assessment of 3rd monthly SSR (period covering 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: chest pain (n= 86, Reporting Odds Ratio [ROR]=4.93) and chest discomfort (n=32, ROR=2.79). A complete signal evaluation was performed after the data cut-off, based on which this signal was refuted, and the SER is presented in Appendix 24.

The global vaccine safety database was queried for ICSRs with PT: Chest pain and/or PT: Chest discomfort. As of the DLP of SSR No. 05 (30-Jun-2022), there were 298 ICSRs of chest pain and/or chest discomfort reported, with a majority of events experienced within 5 days of vaccination, and a majority reported from Australia. There were 25 ICSRs (8.4%) with a seriousness criterion of hospitalisation, life threatening, or disability (not including additional cases that were serious by convention due to IME criteria). Twelve of those ICSRs were cases of myocarditis and/or pericarditis cases and were assessed against a case definition of myocarditis and/or pericarditis. The details of the remaining 13 serious ICSRs are described in a case series in SER included in Appendix 24.

The most frequent MedDRA PTs co-reported with chest pain or chest discomfort were dyspnoea, headache, fatigue, and palpitations. Of the serious cases, the most frequently co-reported events were pericarditis, dyspnoea, and fatigue. Overall, findings of this cumulative review suggest no 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).

15.1.6 Dizziness

A signal of dizziness was validated on 15-Jun-2022 after a request was received from Health Canada in their assessment of 3rd monthly safety update report (period covering 01-Apr-2022 to 30-Apr-2022). A complete signal evaluation was performed after the data cut-off, based on which this signal was refuted, and the SER is presented in Appendix 25.

The global vaccine safety database was queried for ICSRs with PT: Dizziness. As of the DLP of SSR No. 05 (30-Jun-2022), a total of 253 post-marketing ICSRs were retrieved. The majority of ICSRs (89%) were non-serious with 29 (12%) meeting serious criteria. Of those meeting serious criteria, 15 (51%) were due to hospitalisation, and 5 (17%) were medically confirmed. Events were most frequently reported from Germany (45%) and Australia (39%). Time to onset was reported in 176 (70%) cases, occurring most commonly between day 0 and day 5. Dizziness was reported most often by females, in 70% of total events. Co-reported multi-system symptoms were frequently reported, including headache, nausea, diarrhoea, tachycardia, fatigue, pain/chest pain, myalgia, dyspnoea, paraesthesia (pins and needles). In most cases, this constellation of co-

reported symptoms may be associated with reactogenicity, or anxiety, and do not suggest a specific neurologic pattern.

Limited information was provided in most of these reports, including lack of medical history, no information on concurrent medications or vaccination history and no clinical or diagnostic details of the event. No medical treatment was reported for dizziness. There is insufficient information to assess a causal association with Nuvaxovid, and no pattern of co-reported conditions could be identified. SER for dizziness is included in Appendix 25.

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-Jun-2022 are listed in Appendix 26.

15.2.1 Adverse Events of Special Interest (AESI) and Observed-to-Expected (O/E) Analysis

The global vaccine safety database was queried for the following AESI for the interval and cumulative period up to 19-Jun-2022 according to the prespecified search strategies (refer to Appendix 13 for search strategies):

- Acute Disseminated Encephalomyelitis
- Anaphylaxis
- Autoimmune Thyroiditis
- Bell's Palsy
- Cerebral Venous Sinus Thrombosis
- Chronic Fatigue Syndrome
- Encephalitis, Encephalomyelitis
- Fibromyalgia
- Foetal Growth Restriction
- Generalised Convulsions
- Gestational Diabetes
- Guillain-Barré Syndrome
- Haemorrhagic Stroke
- Ischaemic Stroke
- Kawasaki's Disease
- Major Congenital Anomalies
- Maternal Death
- Microcephaly
- Multiple Sclerosis
- Multisystem Inflammatory Syndrome in Children
- Myasthenia Gravis
- Myocardial Infarction
- Myocarditis
- Myocarditis and Pericarditis
- Pericarditis
- Narcolepsy
- Neonatal Death
- Optic Neuritis
- Postural Orthostatic Tachycardia Syndrome
- Preeclampsia
- Preterm Birth
- Rheumatoid Arthritis
- Spontaneous Abortion
- Stillbirth
- Sudden Death
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Transverse Myelitis
- Vaccine-Associated Enhanced Disease
- Venous Thromboembolism

Overview of AESI Results

ICSRs with MedDRA PTs related to the following AESI search strategies have been identified across interval and cumulative data:

- Anaphylaxis (Section 15.1.1)
- Autoimmune Thyroiditis (Section 15.2.1.1)
- Bell's Palsy (Section 15.2.1.2)
- Cerebral Venous Sinus Thrombosis (Section 15.2.1.3)
- Chronic Fatigue Syndrome (Section 15.2.1.4)
- Encephalitis, Encephalomyelitis (Section 15.1.4)
- Fibromyalgia (Section 15.2.1.5)
- Generalised Convulsions (Section 15.2.1.6)
- Guillain-Barré Syndrome (Section 15.2.1.7)
- Haemorrhagic Stroke (Section 15.2.1.8)
- Ischaemic Stroke (Section 15.2.1.9)
- Multiple Sclerosis (Section 15.2.1.10)
- Myocardial Infarction (Section 15.2.1.11)
- Myocarditis and Pericarditis (Section 15.1.2)
- Optic Neuritis (Section 15.2.1.12)
- Postural Orthostatic Tachycardia Syndrome (Section 15.2.1.13)
- Rheumatoid Arthritis (Section 15.2.1.14)
- Spontaneous Abortion (Section 15.2.1.15)
- Thrombocytopenia (Section 15.2.1.16)
- Venous Thromboembolism (Section 15.2.1.17)

Methods for AESI Analysis

O/E analyses are performed for all AESI for which numerator data has been reported. Crude O/E calculations are made prior to adjudication of cases for the purpose of signal generation. Sensitivity analyses are applied for underreporting assuming 50% and 25% of total cases have been reported. Risk windows are applied according to published recommendations, and, where time to onset (TTO) is missing, cases are conservatively assessed to fall within a given risk window. Because TTO is programmatically derived from date-time fields, a more clinically relevant TTO reported in narratives will not be captured programmatically and over inclusion or exclusion of cases may occur. While recognised as an imperfect proxy, the O/E are also run for the subset of medically confirmed ICSRs for a given AESI to refine results against those ICSRs reported by HCPs. Because of the imperfect data impacting O/E results, it is important to note that following the generation of a statistically significant hypothesis generating O/E result,

detailed case series analyses are performed and TTO are refined for descriptive analyses which includes adjudication against case definitions, where available.

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, no follow-up queries for AESI have been issued, including targeted questionnaires for reports of pericarditis and other AESI with statistically significant observed rates greater than expected. NVX has reached out to TGA to seek assistance in obtaining information needed for O/E calculations including uniform ascertainment of time to onset and other AESI-specific elements to fully assess ICSRs against case definitions and to assess causality.
- 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). Although accounting for over half of worldwide exposure, NVX-CoV2373 doses administered in South Korea are excluded from the denominator of O/E, which is expected to bias overall results.

For AESIs that have become validated signals, adjudication against an established case definition (if available) is performed (e.g., Brighton Collaboration case definitions).

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. Limited sample size related to recent market authorization of a new product may reduce the statistical power of these analyses. AE reports with unknown TTO were conservatively included in observed counts and the possibility that 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 publicized media coverage of vaccine safety, provider reporting requirements and increased public awareness. Another consideration for interpretation is lack of administration data for certain regions necessitating use of distribution data to approximate exposure. To minimise differences between populations in question, region-specific background incidence rates were used to calculate overall expected number of reports where available and supplemented by rates from recent, large, multi-centre studies, such as the vACCine COVID-19 monitoring readinESS Project (ACCESS) study (Appendix 10). The potential for differences between the population used to generate the background rate and the population exposed to the vaccine decreasing the comparator validity cannot fully be excluded.

15.2.1.1 Autoimmune Thyroiditis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Acute and chronic thyroiditis.

15.2.1.1.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Thyroiditis (n=1). This AE was non-serious and non-medically confirmed.

This report concerned a 42-year-old female who experienced autoimmune thyroiditis (unknown TTO) with co-reported events of pain and lymph node pain. At the time of reporting, the event outcome was unknown. No other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.1.1.1 Results of the O/E Analysis

- The TTO was not provided in the single AE and was 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 count was lower than the expected count.

15.2.1.1.2 Conclusion

Overall, the co-reported events could be considered confounders in this report. However, with minimal information reported, a causal association cannot be established. This single ICSR conservatively met the TTO inclusion criteria and results of O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.1.2 Bell's Palsy

The global vaccine safety database was queried for interval and cumulative ICSRs based on individual PTs as described in Appendix 13.

15.2.1.2.1 Results and Discussion

A total of 7 ICSRs were retrieved for the interval and cumulative period.

The 7 ICSRs included 8 AEs coded to PTs Facial paralysis (n=4), Bell's palsy (n=3), and Facial paresis (n=1), none of which were medically confirmed. All 8 AEs were serious, of which 1 AE involved hospitalisation. Seven out of 8 AEs were designated as serious by convention, meeting IME criteria, of which 1 AE additionally met other medically important condition criteria.

A serious report of facial paralysis and Bell's palsy occurred in a 47-year-old female with reported medical history of GBS, Headache, Myalgia, Arthralgia, Fatigue, Paralysis, Loss of proprioception, Penicillin anaphylaxis as small child, reaction to flu vaccine and reported concomitant medications of NuvaRing, Fluoxetine, Nurofen, Tramadol, and Panadol. Two days after receiving Nuvaxovid (primary dose 1) she experienced numbness L/H side face and inner ear and tingling/numbness left hand fingertips and was diagnosed with Bell's palsy and possible

onset of Shingles and was prescribed steroids and anti-viral. Diagnostic tests included White blood cell was higher than expected and CRP (C-reactive protein) was slightly elevated at 5.8, MRI (Magnetic resonance imaging) results did not appear to be Bell's Palsy. Treatment included steroids and anti-viral and Nurofen (taken at home as well). At the time of reporting, the outcome of the event of Bell's palsy was unknown and facial paralysis was not resolved. Other reported PTs: Ageusia, Hypoaesthesia, Dry eye, Eye pain, Paraesthesia, Sensory loss, Herpes zoster, Ear inflammation, C-reactive protein increased, White blood cell count increased, Fine motor skill dysfunction, Muscular weakness, Visual impairment, Nervous system disorder, Neuropathy peripheral, Hypertension, Headache.

A report of temporary paresis (coded to MedDRA PT Facial paralysis) occurred in a 55-year-old female who reportedly developed symptoms in the form of hemiparesis and facial paresis on the vaccinated side within 1 hour after vaccination and regressed within 5 days. Relevant medical history included grass pollen allergy, contact dermatitis, and systemic lupus erythematosus. At the time of reporting, the event outcome of facial paralysis was reported as recovered. Furthermore, one report of facial paresis involving hospitalisation (TTO 2 days) in an adult female did not report any significant safety information.

The remaining 4 reports, containing 5 AEs, were for 3 males and 2 females. Reported PTs were Bell’s palsy (n=2), Facial paralysis (n=2), and Facial paresis (n=1). Three of the 5 AEs reported TTO of 0-2 days. No significant details were provided in these reports.

Results of O/E analyses are presented below.

15.2.1.2.1.1 Results of the O/E Analysis

The TTO for 6 of 8 AEs ranged from 0 to 3 days which fell within the risk window of 0-42 days (refer to Table 36). The TTO was not reported for the other 2 AEs and conservatively included in O/E analysis. Therefore, all AEs were conservatively included in the observed count (n=8) for O/E analysis which showed that the observed count was lower than the expected count. However, results were increased and statistically significant when assuming 75% underreporting (RR 2.53, 95% CI: 1.09 – 4.98).

15.2.1.2.2 Limitations of the O/E Analysis

In addition to the general statistical limitations presented in Section 15.2.1, an additional limitation specific to O/E and sensitivity analyses for Bell’s palsy should be considered when interpreting results. One ICSR with 2 events corresponding to a single clinical occurrence of Bell’s palsy but onset documented as 3 days apart was counted as 2 separate instances of the AE in the observed count, falsely inflating the numerator in O/E and sensitivity analyses for Bell’s palsy.

15.2.1.2.3 Conclusion

Although a temporal relationship was seen for 6 AEs, due to a lack of details regarding clinical presentation of Bell's palsy and limited information on diagnostic work-up or medical history, there was insufficient information to establish a causal association. All ICSRs met the TTO inclusion criteria and results of O/E analyses showed lower than the expected background rate, however this rate was increased when assuming 75% underreporting with a statistically significant RR. No safety signal was identified.

15.2.1.3 Cerebral Venous Sinus Thrombosis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Cerebrovascular venous and sinus thrombosis.

15.2.1.3.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Cerebral venous sinus thrombosis (n=1). This AE was designated as serious, meeting IME criteria, LT criteria, and involved hospitalisation. This report concerned a 22-year-old female who experienced CVST, 4 days after vaccination with co-reported events of anisocoria, leg weakness, fever, extreme headache, and extreme limb pain. At the time of reporting, the event outcome was unknown. No other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.3.1.1 Results of the O/E Analysis

The TTO for this single AE was reported as 4 days which fell within the risk window of 0-28 days (refer to Table 36). The observed rate showed an increase that was not statistically significant when compared to the expected rate.

15.2.1.3.2 Conclusion

Overall due to lack of clinical details, no relevant safety information was identified. This report met the TTO inclusion criteria and results of O/E analyses were not statistically significant and fell within expected background rates. No safety signal was identified.

15.2.1.4 Chronic Fatigue Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA PTs: Chronic fatigue syndrome; Post viral fatigue syndrome.

15.2.1.4.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Chronic fatigue syndrome (n=1). This AE was non-serious and non-medically confirmed. This report concerned a 32-year-old male who experienced CFS (unknown TTO) with co-reported events of gastric ulcer, myocarditis, postural orthostatic tachycardia syndrome and tachycardia. At the time of reporting, the event outcome was unknown. No other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.4.1.1 Results of the O/E Analysis

The TTO was not reported for this single AE and 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 count was lower than the expected count.

15.2.1.4.2 Conclusion

No details other than reported event terms were provided in the report, precluding meaningful analysis. This single ICSR conservatively met the TTO inclusion criteria and results of the O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.1.5 Fibromyalgia

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA PT: Fibromyalgia

15.2.1.5.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Fibromyalgia (n=1). This AE was non-serious and medically confirmed. This report concerned an adult male of unspecified age who experienced worsening of pre-existing fibromyalgia (coded to MedDRA PT Fibromyalgia) 2 days after the first dose of vaccination. At the time of reporting, the event outcome for fibromyalgia was not recovered and no other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.5.1.1 Results of the O/E Analysis

The TTO was reported as 2 days for this single AE which fell within risk window of 0-42 days (refer to Table 36). O/E and sensitivity analyses results showed the observed count was lower

than the expected count. Since this single report was medically confirmed, similar result was observed for subset of medically confirmed AE.

15.2.1.5.2 Conclusion

Although a temporal relationship was observed, there was inadequate information to establish a definitive causal association. This single ICSR met the TTO inclusion criteria and results of the O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.1.6 Generalised Convulsions

The global vaccine safety database was queried for interval and cumulative ICSRs using the narrow search strategy; MedDRA SMQ (narrow): Generalised convulsive seizures following immunisation.

15.2.1.6.1 Results and Discussion

A total of 5 ICSRs were retrieved for the interval and cumulative period.

The 5 ICSRs included 5 AEs coded to PTs Seizure (n=3), Clonic convulsion (n=1), and Febrile convulsion (n=1). Four out of 5 AEs were designated as serious by convention, meeting IME criteria, of which 1 AE additionally involved hospitalisation. Three out of 5 AEs were non-medically confirmed.

Of the 5 ICSRs, 4 were for females and 1 was for male; the age range was 19-72 years. One serious, report of clonic convulsions occurred in a 72-year-old female within 10 minutes after vaccination (given as 3rd dose). The convulsions were observed for 3 minutes. Clinical investigations revealed blood pressure 140/90 and pulse 98 while in supine position. Repeated clonic convulsion was observed in the clinic for two to three minutes after which blood pressure was 132/90 and pulse 84. Prior vaccine history against COVID-19 included 1st dose with Comirnaty (COVID-19 Vaccine, mRNA) and the 2nd dose with Vaxzevria (ChAdOx1-S [Recombinant]). At the time of reporting, the event outcome was recovered. Another serious, non-medically confirmed report of seizure, which required hospitalisation, occurred in a 19-year-old male who began to have a fit lasting 10 minutes after waking up in the morning and became unconscious. The fits were characterised as body shaking, unresponsive and trouble breathing. At the time of reporting, the event outcome was not recovered.

The remaining 3 reports concerned females. Reported PTs were Seizure (n=2) and Febrile convulsion (n=1). Two of the 3 reports involved 40 and 44 years old individuals respectively. The TTO for 2 of 3 AEs was 0 days. Overall, no other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.6.1.1 Results of the O/E Analysis

The TTO for 3 out of 5 AEs was reported as 0 days which fell within the risk window of 0-42 days (refer to Table 36). The TTO was not reported for the other 2 AEs and conservatively included in the O/E analyses. Therefore, all AEs were conservatively included in the observed count (n=5) for O/E analyses. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

Two of 5 AEs met inclusion criteria for O/E analysis for medically confirmed reports (n=2), which showed a similar result.

15.2.1.6.2 Conclusion

Although there seemed to be a temporal association in the majority of the reports (n=3), none of these events had sufficient information to support a causal association. All ICSRs met the TTO inclusion criteria and results of the O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.1.7 Guillain-Barré Syndrome

The global vaccine safety database was queried for interval and cumulative ICSRs using the narrow search strategy; MedDRA SMQ (narrow): Guillain-Barré syndrome.

15.2.1.7.1 Results and Discussion

A total of 2 ICSRs were retrieved for the interval and cumulative period according to the search strategy described above.

The 2 ICSRs included 2 AEs coded to PT Guillain-Barré syndrome (n=2). These 2 AEs were designated as serious by convention, meeting IME criteria, of which 1 AE additionally involved hospitalisation.

A single case of GBS involving hospitalisation was reported in a 51-year-old with medical history of polyneuropathy and chemotherapy and with no reported concomitant medications experienced Guillain barre syndrome (GBS) 12 days after receiving Nuvaxovid (primary dose 1). Diagnostic procedures included Magnetic Resonance Imaging (MRI) and cerebrospinal fluid histology which showed no explanation of symptoms. Cerebrospinal fluid (CSF) volume including the histological examination were normal, presence of electrophysiological abnormalities (prolonged distal motor latency) was indicative of mild GBS, symptoms included exacerbation of paraesthesia of extremities, differential diagnosis was a mild form of a sensitive GBS. Treatment with gabapentin was suggested. Autoantibody testing was pending at the time of reporting and the event outcome was not recovered.

A second event reported as probable GBS (MedDRA PT Guillain-Barré syndrome) occurred in a 76-year-old male, 3 days after vaccination with dose 1. At the time of reporting, the event outcome was not recovered. No other significant details were provided.

Results of O/E analyses are presented below.

15.2.1.7.1.1 Results of the O/E Analysis

The TTO for both AEs were reported as 3 days and 12 days respectively which fell within the risk window of 0-42 days (refer to Table 36). The observed rate showed an increase when compared to the expected rate with a non-statistically significant RR. One of 2 AEs met the inclusion criteria for the O/E analysis for medically confirmed AEs (n=1) which showed observed count lower than the expected count.

15.2.1.7.2 Conclusion

One of the 2 reports was confounded by the vaccinee's medical history of polyneuropathy, previous GBS and previous chemotherapy, with no conclusive diagnostic evidence to support diagnoses and the other, lacked relevant safety information. Both ICSRs met TTO inclusion criteria and results of the O/E analyses were not statistically significant and falling within expected background rates. No safety signal was identified.

15.2.1.8 Haemorrhagic Stroke

The global vaccine safety database was queried for interval and cumulative ICSRs using the narrow search strategy; SMQ (narrow): Haemorrhagic central nervous system vascular conditions.

15.2.1.8.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Cerebrovascular accident (n=1). This AE was designated as serious by convention, meeting IME criteria and was non-medically confirmed.

This report of cerebrovascular accident occurred in a 78-year-old female. Co-reported events included atrial fibrillation, dysarthria, and hemiparesis. No other clinically relevant information was provided. At the time of reporting, the event outcome for cerebrovascular accident was not recovered. Note: This report is also discussed in Section 15.2.1.9.1 as it falls under both haemorrhagic stroke and ischaemic stroke search strategies.

15.2.1.8.1.1 Results of the O/E Analysis

The TTO was not reported in this single AE and conservatively assumed to fall within the risk window of 0-28 days (refer to Table 36). O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.2.1.8.2 Conclusion

This single report was confounded by elderly age and co-reported events of atrial fibrillation, dysarthria, and hemiparesis. and lacked pertinent clinical information and diagnostic work-up of haemorrhagic stroke. This single ICSR conservatively met the TTO inclusion criteria and results of O/E analyses showed a lower than expected background rates. No safety signal was identified.

15.2.1.9 Ischaemic Stroke

The global vaccine safety database was queried for interval and cumulative ICSRs using the narrow search strategy; MedDRA SMQ (narrow): Ischaemic central nervous system vascular conditions.

15.2.1.9.1 Results and Discussion

A total of 3 ICSRs were retrieved for the interval and cumulative period

The 3 ICSRs included 3 AEs coded to PTs Brain stem infarction (n=1), Cerebrovascular accident (n=1), and Ischaemic stroke (n=1). All AEs were designated as serious by convention, meeting IME criteria, of which 2 AEs involved hospitalisation. Two of the 3 AEs were non-medically confirmed.

All 3 ICSRs occurred in females; the age range was 48-78 years.

One serious, report of trunk ganglion infarct (coded to MedDRA PT: Brain stem infarction) involving hospitalisation occurred in a 48-year-old female 5 days after vaccination. No description of the event was reported. An MRI was performed, and results were not reported. At the time of reporting, the event outcome was not recovered.

The second report of ischemic stroke involving hospitalisation occurred in a 62-year-old female 21 days after vaccination. Relevant medical history included patent foramen ovale. No other clinically relevant information was provided. At the time of reporting, the event outcome for ischaemic stroke was recovered with sequelae. No other clinically relevant information was provided.

The third report of cerebrovascular accident occurred in a 78-year-old female. Co-reported events included atrial fibrillation, dysarthria, and hemiparesis. No other clinically relevant information was provided. At the time of reporting, the event outcome for cerebrovascular accident was not recovered. Of, note: This report is also discussed in Section 15.2.1.8.1 as it falls under both haemorrhagic stroke and ischaemic stroke search strategies.

Results of O/E analyses are presented below.

15.2.1.9.1.1 Results of the O/E Analysis

TTO was reported for 2 of the 3 AEs as 0 and 28 days respectively; both fell within the risk window of 0-28 days (refer to Table 36). TTO was not reported in the other AE conservatively included in the O/E analysis. Therefore, all AEs were conservatively included in the observed count (n=3) for O/E analysis. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.2.1.9.1.2 Conclusion

These 3 reports lacked pertinent clinical information and diagnostic work-up. All ICSRs met the TTO inclusion criteria and results of O/E analyses showed a lower than expected background rates. No safety signal was identified.

15.2.1.10 Multiple Sclerosis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Multiple sclerosis acute and progressive.

15.2.1.10.1 Results and Discussion

A total of 3 ICSRs were retrieved for the interval and cumulative period.

The 3 ICSRs included 3 AEs coded to PTs Multiple sclerosis relapse (n=2) and Multiple sclerosis (n=1). All AEs were designated as serious by convention, meeting IME criteria, of which 1 AE additionally met disability criteria. Two out of 3 AEs were non-medically confirmed.

Of the 3 ICSRs, 2 were for females and 1 was for male; the age range was 36-63 years.

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.

15.2.1.10.1.1 Results of the O/E Analysis

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

included in O/E analyses. Therefore, all AEs were conservatively included in the observed count (n=8) for O/E analysis. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

One of the 3 AEs met inclusion criteria for O/E analysis for medically confirmed AEs (n=1) which showed a similar result.

15.2.1.10.2 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 background rates. No safety signal was identified.

15.2.1.11 Myocardial Infarction

The global vaccine safety database was queried for interval and cumulative ICSRs using the narrow search strategy of MedDRA SMQ (narrow): Myocardial infarction.

15.2.1.11.1 Results and Discussion

A total of 8 ICSRs were retrieved for the interval and cumulative period.

The 8 ICSRs included 8 AEs coded to PTs Troponin increased (n=5) and Myocardial infarction (n=3). Six out of 8 AEs were designated as serious by convention, meeting IME criteria, of which 2 AEs additionally involved hospitalisation. Of the total 8 AEs, 6 were non-medically confirmed.

Of the 8 ICSRs, 5 were for males and 3 for females; the age range was 24-93 years. Each of the 3 events of myocardial infarction occurred in elderly men, additional risk factors were not reported. Three reports of troponin increased included possible alternative explanations, e.g., costochondritis/physical exertion. One report of troponin increased occurred in a 76-year-old female concurrently taking anti-hypertensives and lipid-lowering medications (though medical history was not reported); myopericarditis was co-reported, but no diagnostic details were provided. No clinical pattern or complete safety assessment could be ascertained due to confounders or missing information, such as medical history and/or concomitant medications.

Results of O/E analyses are presented below.

15.2.1.11.1.1 Results of the O/E Analysis

The TTO for 4 of 8 AEs ranged from 0 to11 days and fell within the risk window of 0-28 days (refer to Table 36). TTO was not reported in the other 4 AEs and conservatively included in the O/E analysis. Therefore, all AEs were conservatively included in the observed count (n=8) for O/E analyses. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

Two of 8 AEs met inclusion criteria for the O/E analysis for medically confirmed AEs (n=2) which showed similar results.

15.2.1.11.2 Conclusion

Confounders included elderly age, co-reported events or medical history in these reports. 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 background rates. No safety signal was identified.

15.2.1.12 Optic Neuritis

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA PT: Optic neuritis.

15.2.1.12.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Optic neuritis (n=1). This AE was designated as serious by convention, meeting IME criteria, and was non-medically confirmed.

This report concerned a 36-year-old female who experienced optic neuritis 10 days after vaccination with co-reported events of lethargy, hyperhidrosis, and ear congestion. This female presented with blurred vision, associated pain during movements in the right eye, headaches, eye inflammation on the right side, and muffled hearing. 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. Prednisone was prescribed as treatment. The event outcome for optic neuritis was reported as not recovered.

Results of O/E analyses are presented below.

15.2.1.12.1.1 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 count was lower than the expected count.

15.2.1.12.2 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 background rates. No safety signal was identified.

15.2.1.13 Postural Orthostatic Tachycardia Syndrome

The global vaccine safety database was queried for interval and cumulative ICSR using the specific MedDRA PT: Postural orthostatic tachycardia syndrome.

15.2.1.13.1 Results and Discussion

A single ICSR was retrieved for the interval and cumulative period.

The single ICSR included 1 AE coded to PT Postural orthostatic tachycardia syndrome (n=1). This AE was non-serious and non-medically confirmed.

This report concerned a 32-year-old male who experienced POTS with co-reported events of gastric ulcer (IME), myocarditis (hospitalisation), chronic fatigue syndrome, and tachycardia. No description of the event was reported. At the time of reporting, the event outcome was unknown.

Results of O/E analyses are presented below.

15.2.1.13.1.1 Results of the O/E Analysis

The TTO was not provided in the single AE and was 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 count was lower than the expected count.

15.2.1.13.2 Conclusion

No information on diagnostic details or concomitant medications were provided in the report, precluding meaningful analysis. This single ICSR conservatively met the TTO inclusion criteria and results of O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.1.14 Rheumatoid Arthritis

The global vaccine safety database was queried for interval and cumulative ICSR using the specific MedDRA HLT: Rheumatoid arthritis and associated conditions and PT: Polyarthritis.

15.2.1.14.1 Results and Discussion

A total of 3 ICSRs were retrieved for the interval and cumulative period.

The 3 ICSRs included 3 AEs coded to PT Rheumatoid arthritis (n= 3). All the AEs were designated as serious by convention, meeting IME criteria and were not medically confirmed.

Of the 3 ICSRs, 2 were for females and 1 was for male. The age was reported in only 2 of 3 ICSRs as 29 and 46 years respectively.

In one report, a 29-year-old female with a medical history of arthralgia and axial spondylarthritis experienced rheumatoid arthritis aggravated (coded to MedDRA PT: Rheumatoid arthritis) along with limb discomfort on the same day after receiving the vaccine. In a second report, a 46-year-old male experienced aggravation of rheumatoid arthritis (reported as 'drastic deterioration of rheumatoid arthritis, which had previously been dormant for years') (coded to MedDRA PT: Rheumatoid arthritis), after receiving the primary dose of the vaccine. A third report concerned a female of unknown age and was received with minimal information. No diagnostic tests or laboratory markers were provided in any of the reports.

Results of O/E analyses are presented below.

15.2.1.14.1.1 Results of the O/E Analysis

- The TTO for 2 of 3 AEs were reported as 0 days 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 AEs and conservatively included in O/E analysis. Therefore, all AEs were conservatively included in the observed count (n=3) for O/E analysis. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.2.1.14.2 Conclusion

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

15.2.1.15 Spontaneous Abortion

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLTs: Abortions spontaneous; Abortions not specified as induced or spontaneous.

15.2.1.15.1 Results and Discussion

A total of 4 ICSRs were retrieved for the interval and cumulative period.

The 4 ICSRs included 4 AEs coded to PT Abortion spontaneous (n = 4). All 4 AEs were designated as serious by convention, meeting IME criteria and were not medically confirmed.

In one report, a 23-year-old female, at one month of gestation presented with paraesthesia 2 days after vaccination and subsequently experienced spontaneous abortion 2 weeks later. No other significant details were provided. The other 3 ICSRs involved females with age ranging from 28-31 years. TTO was reported in only 2 out of 4 AEs as 0 and 33 days respectively. No significant medical history, concomitant medication, laboratory tests, or diagnostic procedures were provided.

No O/E analysis could be performed for spontaneous abortion as the exposure is unknown in Women of Child-Bearing Age (WOCBA).

15.2.1.15.2 Conclusion

A meaningful analysis could not be performed as vaccination with respect to pregnancy was mostly not reported except for one report where a female at gestational period of 1 month presented with paraesthesia and spontaneous abortion. Other details like obstetric and medical history, concomitant medications, and further details were lacking. Hence the available information was not suggestive of a causal association between the event and vaccine. No safety signal was identified.

15.2.1.16 Thrombocytopenia

The global vaccine safety database was queried for interval and cumulative ICSR using the specific MedDRA HLT: Thrombocytopenias.

15.2.1.16.1 Results and Discussion

A total of 5 ICSRs were retrieved for the interval and cumulative period.

The 5 ICSRs included 6 AEs coded to PT 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 1 met other medically important condition criteria. Four out of 6 AEs were non-medically confirmed. All reports occurred in females.

Of the 5 ICSRs, the age range for 4 of 5 reports was 23-50 years. One report of thrombocytopenia concerned a 50-year-old. Medical history included degenerative bone disease, gastro-oesophageal reflux disease, hypertension, hypothyroidism, immune-mediated thyroiditis, and irritable bowel syndrome. Concomitant medication included L-thyroxin, lercanidipine, ramipril and opipramol. Another report concerned a 32-year-old female who presented with significant deterioration of existing thrombocytopenia (coded to MedDRA PT Thrombocytopenia) 7 days after receiving the first dose of vaccination. Co-reported event included increased tendency to bruise. Medical history included Hashimoto’s disease with hypothyroidism and autoimmune-mediated thrombocytopenia. No relevant safety information was reported in the other 3 reports.

Results of O/E analyses are presented below.

15.2.1.16.1.1 Results of the O/E Analysis

- The TTO for 4 of 6 AEs ranged from 7-34 days which fell within the risk window of 0-42 days (refer to Table 36). TTO was not reported in the other 2 AEs and were conservatively included in O/E analyses. One of the reports identified two AEs coded to PTs Immune thrombocytopenia and Thrombocytopenia which reportedly occurred on the same day and

hence were pooled in one report for the O/E analysis. Therefore, after pooling two AEs into one report, 5 AEs met inclusion criteria for the observed count (n=5) for O/E analysis. O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

Two of 6 AEs met inclusion criteria for the O/E analysis for medically confirmed AEs (n=2) which showed similar result.

15.2.1.16.2 Conclusion

Confounding factors included medical history and concomitant medication in 2 reports. Overall, 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 background rates. No safety signal was identified.

15.2.1.17 Venous Thromboembolism

The global vaccine safety database was queried for interval and cumulative ICSR using the narrow search strategy; SMQ (narrow): Embolic and thrombotic events, venous prespecified.

15.2.1.17.1 Results and Discussion

A total of 9 ICSRs were retrieved for the interval and cumulative period.

The 9 ICSRs included 9 AEs coded to PTs Pulmonary embolism (n=4), Thrombophlebitis (n=3), Cerebral venous sinus thrombosis (n=1), and Deep vein thrombosis (n=1). Seven of the 9 AEs were designated as serious by convention, meeting IME criteria, of which 4 AEs additionally involved hospitalisation, and 2 met LT criteria. Five of the 9 AEs were medically confirmed.

Of the 9 ICSRs, 7 were for females and 2 for males; the age range for 8 of 9 reports was 22-85 years.

One report of pulmonary embolism (TTO 9 days) involving hospitalisation concerned an 85-year-old female with risk factors of third degree atrioventricular (AV) block, use of artificial cardiac pacemaker, and cardiac failure. COVID-19 vaccine history included dosing with 4 doses of Spikevax (COVID-19 Vaccine, mRNA). Another report of pulmonary embolism (TTO 23 days) involving hospitalisation concerned a 29-year-old male and co-suspect medications included Loxapac (loxapine) and alprazolam. No relevant safety information was reported in the other 3 reports of thrombophlebitis, 2 reports of pulmonary embolism, and 2 reports of deep vein thrombosis. No clinical pattern or complete safety assessment could be ascertained due to missing information, such as medical history and/or concomitant medications.

Results of O/E analyses are presented below.

15.2.1.17.1.1 Results of the O/E Analysis

- The TTO for all AEs ranged from 1-23 days which fell within the risk window of 0-28 days (refer to Table 36). O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

Five of 9 AEs met inclusion criteria for the O/E analysis for medically confirmed AEs (n=5) which showed similar result.

15.2.1.17.2 Conclusion

Confounding factors included the elderly age group in 2 reports, co-reported events in 3 reports, medical history of AV block with pacemaker use in 1 report, and co-suspect drugs in 1 report. Overall, 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 background rates. No safety signal was identified.

15.2.2 Additional Safety Topics for Monitoring

The global vaccine safety database was queried for the cumulative period up to 19-Jun-2022 according to the prespecified search strategies for the safety topics listed below (refer to Appendix 14 for search strategy of safety topics).

- Fatal reports (refer to Section 15.2.2.1)
- Experience in special patient populations (paediatric and elderly age groups [refer to Section 15.2.2.2])
- Pregnancy (refer to Section 16.3.6.1)
- Vaccine anxiety-related reactions (refer to Section 15.2.2.3)
- Cholecystitis (refer to Section 15.2.2.4)
- Inflammatory eye disorders (refer to Section 15.2.2.5)
- Menstrual disorders (refer to Section 15.2.2.6)
- Paraesthesia (refer to Section 15.1.3)
- Reactogenicity profile- second dose and boosters (based on impurity levels) (refer to Section 15.2.2.7)

15.2.2.1 Fatal Reports

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; Seriousness criteria: Death OR Event Outcome = Fatal.

15.2.2.1.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 1 ICSR involving a fatal outcome (Refer to Appendix 19). This was a serious, medically confirmed AE coded to PT Concomitant disease aggravated (n=1).

This report concerned a 96-year-old male with medical history of cerebrovascular accident, congestive heart disorder, atrial fibrillation, dementia with Lewy bodies, Parkinson's disease, and type 2 diabetes mellitus. Due to lacking TTO, a temporal relationship could not be identified. No other relevant information was reported. No new information was received upon follow-up.

Results of O/E analyses are presented below.

15.2.2.1.1.1 Results of O/E Analysis

The risk window identified for fatal reports was 0 to 999 days (refer to Table 36). This single AE met the inclusion criteria for the observed count for both cumulative AE and medically confirmed AE for O/E analysis (n=1). O/E and sensitivity analyses results showed that the observed count was lower than the expected count.

15.2.2.1.2 Conclusion

A temporal relationship could not be identified due to lacking TTO. When considering the confounding factors of medical history and elderly age of the individual, the single AE of concomitant disease aggravated in this report did not raise any safety concerns. This ICSR met TTO inclusion criteria and results of O/E analyses showed lower than expected background rates. No safety signal was identified.

15.2.2.2 Experience in Special Patients Populations

15.2.2.2.1 Age group: Paediatrics

Experience in paediatric populations is a safety topic under surveillance due to the population's underrepresentation in clinical studies.

The global vaccine safety database was queried to include all ICSRs involving paediatric patients < 18 years of age.

15.2.2.2.1.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 12 ICSRs involving paediatric patients (<18 years of age) which contained a total of 25 AEs including 3 non-serious, medically confirmed AEs; and 22 non-serious, non-medically confirmed AEs.

The most frequently reported PTs were Vaccination error (n=11) and Product administered to the patient of inappropriate age (n=8). Of the 12 ICSRs, 8 were for males, 3 for females and 1 was of unknown gender; the age range was 9-17 years. The majority of the AEs were non-medically confirmed and non-serious (22, 73.4%). No other significant details were reported for the majority of ICSRs.

The rr of events within paediatric population was 1.16 per 100,000 doses administered, equivalent to 0.00116% of all doses administered.

15.2.2.2.1.2 Conclusion

A review of these reports did not suggest any trends in AEs particular to this population compared to the AE profile as defined in the CCDS for the overall population. No safety signal was identified.

15.2.2.2.2 Age group: Elderly

Experience in elderly populations is a safety topic under surveillance to monitor any trends in AEs occurring in this population in the post-marketing setting.

The global vaccine safety database was queried include all ICSRs involving elderly patients ≥65 years of age.

15.2.2.2.2.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 145 ICSRs involving elderly patients (≥ 65 years of age) which contained a total of 500 AEs including 1 fatal, 31 serious and 38 non-serious, medically confirmed AEs; and 49 serious and 381 non-serious, non-medically confirmed AEs.

The most frequently reported PTs were Headache (n=31), Fatigue (n=25) and Myalgia (n=19). Of the 145 reports, 40 were for males and 100 for females; the age range was 65-96 years. TTO ranged from 0-61 days when reported (n=87) and in half of the reports, it ranged within 0-10 days (n=74, 51%). Of the total 500 AEs reported, most of the AEs were non-serious, non-medically confirmed (n=381, 76.2%). The outcome of the majority of the events were reported as not recovered at the time of reporting. No significant medical history or concomitant medications were reported for the majority of the ICSRs.

15.2.2.2.2.2 Conclusion

A review of these reports did not suggest any trends in AEs particular to this population compared to the AE profile as defined in the CCDS for the overall population. No safety signal was identified.

15.2.2.3 Vaccine Anxiety-Related Reactions

Vaccine anxiety-related reactions is a safety topic under surveillance to monitor any anxiety related events post vaccination in post-marketing setting.

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLT: Anxiety symptoms.

15.2.2.3.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 22 ICSRs of vaccine anxiety-related reactions which contained a total of 22 AEs coded to PTs Anxiety (n=16), Nervousness (n=3), Agitation (n=2), and Tension (n=1) including 2 non-serious, medically confirmed AEs; and 1 serious and 19 non-serious, non-medically confirmed AEs.

Of the 22 reports, 2 were for males and 20 for females; the age range was 27-62 years. The TTO ranged from 0-17 days when reported (n=14). No significant medical history or concomitant medications were reported for the majority of ICSRs.

The rr was 2.127 per 100,000 doses administered, equivalent to 0.00213% of all doses administered.

15.2.2.3.2 Conclusion

A review of these reports did not reveal any trends in any anxiety related reactions post vaccination. No safety signal was identified.

15.2.2.4 Cholecystitis

Cholecystitis is a safety topic under surveillance due to insufficient information obtained from clinical studies.

The global vaccine safety database was queried for interval and cumulative ICSRs using the MedDRA HLT: Cholecystitis and cholelithiasis; SMQ: Functional, Inflammatory and Gallstone Related Biliary Disorders.

15.2.2.4.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 6 ICSRs meeting the prespecified search strategy for cholecystitis which contained a total of 6 AEs including 1 serious, medically confirmed; 4 non-serious and 1 serious, non-medically confirmed.

The most frequently reported PTs were Abnormal faeces (n=2) and Jaundice (n=2). Of the 6 ICSRs, 3 were for males and 3 for females; the age range was 23-54 years. TTO ranged from 0-12 days when reported (n=4). The majority of the AEs were non-serious, non-medically confirmed (n=4, 66.6%). Two reports had medical history reported, 1 of which included Crohn’s

Disease and the other included seasonal allergy and mild expression. The specific reports with hospitalisations were summarised in Table 25. No other significant details were provided. The report characteristics and demographics are described in Table 23 and Table 24 respectively.

The rr was 0.58 per 100,000 doses administered, equivalent to 0.00058% of all doses administered.

Table 23: Cholecystitis Report Characteristics

Report Characteristics			
		n	**%**
Total Reports Retrieved		6	100
Total ICSR included in summary tables		6	100
Report Origin	Australia	3	50
	Germany	2	33.3
	New Zealand	1	16.7
Seriousness Criteria (n=6)	Hospitalisation*	3	50
	Fatal	0	0
	Non-serious	4	50
MedDRA Terms (n=6)	Jaundice	2	33.3
	Faeces pale	1	16.7
	Abnormal faeces	2	33.3
	Blood bilirubin increased	1	16.7
Event Latency (n=6)	0-5 days	3	50
	6-10 days	0	0
	Over 10 days	1	16.7
	Unknown	2	33.3
Event Outcome (n=6)	Not Recovered/Not Resolved at time of initial report	2	33.3
	Recovered/Resolved	2	33.3
	Unknown	2	33.3

*:One report involving hospitalisation (4.1(b)) was reported as a non-serious report, hence an overlap in count was observed.

Table 24: Cholecystitis Demographics

Gender	**All Reports[a]**	
	n=6	**% of Total**
Female	3	100
40-49	1	33.3
50-59	1	33.3
Unknown	1	33.
Male	3	100
20-29	1	33.3
30-39	1	33.3
40-49	1	33.3

[a]:Search strategy: HLT: Cholecystitis and cholelithiasis, SMQ (Broad): Functional, inflammatory and gallstone related biliary disorders, SMQ (Narrow): Functional, inflammatory and gallstone related biliary disorders Cumulative to 19-Jun-2022

Table 25: Cholecystitis Serious Report Details

Case #	Brief Narrative	Co-reported Symptoms	Preferred Term/s with Reported Verbatim	Outcome	TTO	Medical History
4.1(b)	23-year-old male from 4.1(b) reported blood bilirubin increased. Hospitalisation selected for events Blood bilirubin increased, Chest discomfort, Chest pain, Dizziness, Malaise, Mitral valve thickening and Palpitations and Medically significant selected for events Electrocardiogram abnormal and Tachycardia. Echocardiogram (Result: with abnormal results, 50% prolapse with significant thickening of the mitral valve leaflet tip, mild to moderate regurgitation), DNA Antibody (Result: 705-175 on anti-DNA-sb-blood test), Liver function test (Result: 55 bilirubin levels) and Blood test (Result: indicated recent infection/bug).	Chest discomfort, Chest pain. Dizziness, Malaise, Mitral Valve thickening, Palpitation, Pericarditis, Tachycardia	Blood Bilirubin Increased (Blood bilirubin increased)	Unknown	Unknown	Not reported
4.1(b)	A female with age unknown from 4.1(b) reported Jaundice with other accompanying symptoms and was hospitalised in Mar-2022 and discharged in Apr-2022.	Dysgeusia, Headache, Flatulence, Intestinal haemorrhage, Dehydration, Rectal Scab, Hypotension	Jaundice (Little jaundiced)	Not recovered	Unknown	Crohn's disease
4.1(b)	A 38-year-old male from 4.1(b) reported Jaundice. After vaccination, almost immediately, intense itching 24 hours a day Approximately 8MAR22 diagnosed jaundiced, GP referred patient to hospital and admitted on 15MAR22. Liver biopsy 21/322 – result consistent with drug/toxin-induced injury. Individual experienced ongoing pain in hospital following biopsy until time this report was submitted.	Pruritus	Jaundice (Jaundice)	Not recovered	13 days	Not reported

15.2.2.4.2 Conclusion

Although there was a temporal association reported in half of the reports (n=3), there was no other relevant safety information to establish a causal association. No safety signal was identified.

15.2.2.5 Inflammatory Eye Disorders

Inflammatory eye disorders is a safety topic under surveillance due to insufficient information obtained from clinical studies.

The global vaccine safety database was queried for interval and cumulative ICSRs using the prespecified search strategy for inflammatory eye disorders (refer to Appendix 14).

15.2.2.5.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 33 ICSRs meeting the prespecified search strategy for inflammatory eye disorders which contained a total of 38 AEs including 2 non-serious medically confirmed AEs, 34 non-serious, non-medically confirmed and 2 serious non-medically confirmed AEs.

The most frequently reported PTs were Eye swelling (n=9), Lacrimation increased (n=5), Ocular hyperaemia (n=4) and Photophobia (n=5). Of the 33 reports, 26 were for females and 7 for males; the age range was 26-61 years. The TTO for most of these reports ranged from 0-3 days (n=13). Most of the AEs were non-serious, non-medically confirmed (n=34, 89.47%). The majority of the events were reported as not recovered at the time of reporting.

Medical history in these reports included seasonal allergy (n=4), asthma (n=2) and Basedow's disease (n=2). No other significant details were provided.

The rr was 3.19 per 100,000 doses administered, equivalent to 0.00319% of all doses administered.

15.2.2.5.2 Conclusion

A review of these reports did not reveal a causal association due to insufficient information. No safety signal was identified.

15.2.2.6 Menstrual Disorders

Menstrual disorder is a safety topic under surveillance due to insufficient information obtained from clinical studies

The global vaccine safety database was queried for interval and cumulative ICSRs using the specific MedDRA HLGT: Menstrual cycle and uterine bleeding disorders.

Based on a request that was received from PRAC, pursuant to EMA PRAC assessment of SSR No. 04 (period covering 01-May-2022 to 31-May-2022), the safety topic of menstrual disorders became a validated signal after the cut-off date of this report and is considered late-breaking information. A complete review (SER) was appended to SSR No. 06.

15.2.2.6.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 66 ICSRs meeting the prespecified search strategy for menstrual disorders which contained a total of 104 AEs including 1 serious, medically confirmed AE; and 5 serious and 98 non-serious non-medically confirmed AEs.

The age of these females ranged from 20 to 53 years. TTO ranged from 0-35 days when reported (n=37).

Of the total 104 AEs reported, the predominantly reported PTs included Menstrual disorder (n=37), Heavy menstrual bleeding (n=18), Menstruation irregular (n=10), Amenorrhea (n=9), Dysmenorrhea (n=9), Intermenstrual bleeding (n=7). Most of the AEs were non-serious, non-medically confirmed (n=98, 94%). The outcome of majority of the events were reported as not recovered at the time of reporting. TTO ranged from 0-5 days for most reports with TTO (n=22).

There were 3 serious ICSRs which contained 6 AEs. There was one medically confirmed serious report which concerned a 39-year-old female who experienced hypomenorrhoea with co-reported event of cardiac disorder and involved hospitalisation. Concomitant medication of Caprilon (tranexamic acid) was also reported. The other 5 serious, non-medically confirmed AEs included heavy menstrual bleeding (n=2), menstrual disorder (n=2), and menstruation irregular (n=1). A summary of these 3 ICSRs is presented in Table 26.

The rr was 6.38 per 100,000 doses administered, equivalent to 0.00638% of all doses administered.

Table 26: Menstrual Disorders ICSR Case Listing: Serious ICSRs and ICSRs with PT Heavy Menstrual Bleeding (Cumulative)

Case Number	Country	Brief Narrative	Preferred Term/s with Reported Verbatim	Serious Criteria	TTO	Medical and Menstrual History	Treatment
Menstrual Disorders Serious ICSRs							
4.1(b)	4.1(b)	A 32-year-old, female experienced Heavy menstrual bleeding, Menstrual disorder, Menstruation irregular along with chest pain after receiving Nuvaxovid 10 ug/mL primary dose on an unspecified date. No medical history was reported. The outcome of the event was unknown.	Heavy menstrual bleeding (heavy menstrual bleeding); Menstrual disorder (menstrual disorder); Menstruation irregular (menstruation irregular)	Medically Significant	Not reported	Not reported	Not reported
4.1(b)	4.1(b)	A 38-year-old female with medical history of abdominal pain, chest pain (leading to hospital admission), chills, diarrhoea, dyspnoea, headache, hyperhidrosis, hypoaesthesia, palpitations, tachycardia, and vomiting- after administration of Comirnaty on 04-JUL-2021 experienced Cardiac disorder, Heavy menstrual bleeding and Menstrual disorder after vaccination with Nuvaxovid. Treatment for the events was not reported. The outcome was not resolved.	Heavy menstrual bleeding (heavy menstrual bleeding); Menstrual disorder (menstrual disorder); Cardiac Disorder (cardiac disorder)	Hospitalisation and Medically Significant for Menstrual disorder	Unknown	Abdominal pain, Chest pain Chills, Diarrhoea, Dyspnoea, Headache, Hyperhidrosis, Hypoaesthesia, Palpitations, Tachycardia Vomiting after administration of Comirnaty on 04-JUL-2021	Not reported

Table 26: Menstrual Disorders ICSR Case Listing: Serious ICSRs and ICSRs with PT Heavy Menstrual Bleeding (Cumulative)

Case Number	Country	Brief Narrative	Preferred Term/s with Reported Verbatim	Serious Criteria	TTO	Medical and Menstrual History	Treatment
4.1(b)	4.1(b)	A 39-year-old female, experienced Hypomenorrhoea, one day after receiving Nuvaxovid. The concomitant medications included: Nasonex (mometasone furoate monohydrate) nasal spray, suspension 4.1(b) (tranexamic acid) tablet as necessary and 4.1(b) (Ibuprofen). Treatment for the event was not reported. The outcome was not resolved.	Hypomenorrhoea (light periods); Vaccination site haematoma (vaccination site haematoma); Exercise tolerance decreased (exercise tolerance decreased); Asthenia (asthenia); Arrhythmia (arrhythmia); COVID-19 immunisation (revaccination with different covid-19 vaccine); Confusional state (confusion); Pyrexia (pyrexia); Headache (headache); Influenza like illness (flu-like symptoms); Sinus node dysfunction (sinus node dysfunction); Dyspnoea (dyspnoea); Pulmonary pain (pulmonary pain); Tachycardia (tachycardia); Fatigue (fatigue); and Myokymia (myokymia)	Hospitalisation	1 day	Not reported	Not reported

15.2.2.6.2 Conclusion

This safety topic became a validated signal and underwent signal evaluation; the SER was provided in SSR No. 06.

15.2.2.7 Reactogenicity Profile-Second Dose and Boosters (based on impurity levels)

Reactogenicity profile-second dose and booster is a safety topic under surveillance to monitor any trends in reactogenicity based on impurity levels after second or booster dose in the post-market setting.

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 14).

15.2.2.7.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 76 ICSRs meeting the prespecified search strategy for reactogenicity profile-second dose and boosters which contained a total of 450 AEs. Of these 76 ICSRs, one report with a missing batch number was excluded from the analysis.

The most frequently reported PTs were coded to Headache (n=34), Fatigue (n=27), Pyrexia (n=25), Limb discomfort (n=19) and Injection site pain (n=17). Of the 76 ICSRs, 54 were for females and 22 for males; the age range was 21-93 years. TTO from second dose or boosters ranged from 0-24 days. The majority of the AEs were non-medically confirmed; non-serious (n=354, 77.8%) with most of the outcomes reported as recovering; recovered at the time of reporting.

No batch related issues were identified in any of the reports.

The rr was 7.35 per 100,000 doses administered, equivalent to 0.00735% of all doses administered.

15.2.2.7.2 Conclusion

A review of ICSRs did not identify any trend related to reactogenicity based on impurity levels specifically after a second dose and/or a booster. 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 v1.0.

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

Risk Criteria	Description
Important identified risk(s)	None
Important potential risk(s)	VAED, including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis 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) V1.0 dated 20-Dec-2021

At the request of the EMA on 04 March 2022, anaphylaxis was removed as an important potential risk and recharacterised to a risk considered not important for inclusion in the EU RMP V1.1 (submitted 29-Mar-2022) based on EMA feedback that “The experience with available vaccines shows that Anaphylaxis, while remaining an identified risk for the product, as with any other biologicals, does not have a considerable impact on the risk/benefit balance”. Furthermore, “cumulative data from post-marketing use for other COVID-19 vaccines besides Nuvaxovid shows that the risk mitigation activities included in the Product Information are well adhered to, and events are managed adequately in clinical practice”. The EU RMP was approved on 01-Jul-2022 by way of approval of the Type II variation to include adolescents.

On 17-May-2022, EU RMP V1.2 was submitted to EMA to support the extension of the posology to include booster dosing. There were no changes to the important safety concerns from EU RMP V1.1 to EU RMP V1.2.

A summary of the important safety concerns at the end of the reporting interval are provided in, Table 28 consistent with EU RMP V1.2.

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

Risk Criteria	Description
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 RMP v1.2 dated 09-May-2022.

16.2 Signal Evaluation

During the reporting interval and cumulatively, there were no signals that were closed upon evaluation.

Signal evaluations were completed for anaphylaxis, myocarditis/pericarditis, and paraesthesia for NVX-CoV2373. The anaphylaxis and paraesthesia signals have been confirmed; myocarditis/pericarditis had been assessed as indeterminate signal at cut-off date and remained an important potential risk until confirmed as an important identified risk on 03-Aug-2022 (post cut-off date). Analyses of these topics as of 19-Jun-2022 is presented in Section 15.1 and SER completed following the cut of date of this report are provided in Appendix 20, Appendix 21 , and Appendix 22 respectively.

16.3 Evaluation of Risks and New Information

The following subsections present the following:

- New information on important potential risks – Section 16.3.1
- New information on important identified risks – Section 16.3.2
- New information on other potential risks not categorised as important – Section 16.3.3
- New information on other identified risks not categorised as important – Section 16.3.4
- Update on important missing information – Section 16.3.6

16.3.1 New Information on Important Potential Risks

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

There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD.

16.3.1.1.1 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 14).

16.3.1.1.2 Conclusion

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

16.3.1.2 Anaphylaxis

A signal of anaphylaxis was validated on 18-May-2022. An SER was completed following the cut-off date for this report, and the NVX Safety Review Team confirmed anaphylaxis as an identified risk (refer to Appendix 20).

16.3.1.2.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the MedDRA SMQ (Narrow): Anaphylactic reaction.

16.3.1.2.2 Conclusion

Most reports retrieved for the interval and cumulative period, have originated from HAs (n=19/20), thus limiting NVX's ability to obtain Targeted Follow-up Questionnaires (TFQs). For reports from TGA (n=13/20), under the pandemic setting, they receive reports directly through enhanced reporting mechanisms and there is no mechanism for NVX to execute targeted queries to reporters to obtain information that would enable more complete case assessment.

Further details and analysis are presented in Section 15.1.1.

16.3.1.3 Myocarditis and Pericarditis

Myocarditis and pericarditis have been recognised as a rare complication of mRNA COVID-19 vaccines. Although myocarditis has also been reported after administration of a number of vaccines for viral infections, reported rates are lower than the rates after mRNA vaccines and the reported rates are considered to be similar to expected background rates.

A signal of myocarditis/pericarditis was validated on 05-May-2022 based on HA requests and statistically significant results of O/E analyses in the cumulative period. An SER was completed following the cut-off date for this report and is presented in Appendix 21.

16.3.1.3.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the MedDRA SMQ (narrow): Non-infectious myocarditis/pericarditis, HLTs: Non-infectious myocarditis; Non-infectious pericarditis.

16.3.1.3.2 Conclusion

All reports retrieved (n=44) for the interval and cumulative period, have originated from HAs, thus limiting NVX's ability to obtain TFQ. For reports from TGA (n=36/44), under the pandemic setting, they receive reports directly through enhanced reporting mechanisms and there is no mechanism for NVX to execute targeted queries to reporters to obtain information that would enable more complete case assessment.

Following the cut-off date of 19-Jun-2022, myocarditis/pericarditis was confirmed as an important identified risk. The planned labelling updates are presented in Section 14.2.

Further details and analysis are presented in Section 15.1.2.

16.3.2 New Information on Important Identified Risks

During the reporting interval and cumulatively, there were no important identified risk(s) for NVX-CoV2373.

16.3.3 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)

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

During the reporting interval and cumulatively, there were no identified risks for NVX-CoV2373.

16.3.5 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 broad search strategy; MedDRA SMQ (broad): Lack of efficacy/effect.

The following definition[7] 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.

16.3.5.1 Results and Discussion

During the reporting interval and cumulatively, the database query identified 1 ICSR meeting the prespecified search strategy for vaccination failures / lack of efficacy. This report contained a non-serious, non-medically confirmed AE coded to PT Paradoxical drug reaction (n=1) occurring in a 27-year-old female.

The event occurred 2 days after the primary dose of the vaccine. Since the full dose schedule was not completed, this report was assessed as not a vaccination failure.

The rr was 0.0967 per 100,000 doses administered, equivalent to 0.00096% of all doses administered.

16.3.5.2 Conclusion

Since the event of paradoxical drug reaction occurred prior to completing the full dose schedule, it was assessed as not a case of vaccination failure. No safety signal was identified.

16.3.6 Update on Missing Information Topics

16.3.6.1 Update on Missing Information Topic: 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 excreted in human milk.

16.3.6.1.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in pregnancy and while breastfeeding (refer to Appendix 14).

16.3.6.1.2 Results and Discussion

Use in Pregnancy: During the reporting interval and cumulatively, the database query identified 4 ICSRs meeting the prespecified search strategy for use in pregnancy. The 4 ICSRs involving pregnancy identified a total of 5 AEs coded to PTs Abortion spontaneous (n=4) and Paraesthesia (n=1) including 4 serious and 1 non-serious, non-medically confirmed AEs.

All 4 reports were retrospective in nature. Age of the females ranged from 23-31 years. 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 ages of the females ranged from 23-31 years. The TTO ranged from 0-33 days when reported (n=3). Further discussion of these ICSRs is found in Section 15.2.1.15.

Use while breastfeeding: During the reporting interval and cumulatively, the database query identified 2 ICSRs meeting the prespecified search strategy for use while breastfeeding. The 2 ICSRs identified a total of 2 AEs coded to PTs Lactation puerperal increased (n=1) and Suppressed lactation (n=1). Both AEs were non-serious and non-medically confirmed.

The event outcomes in the two reports were recovered and not recovered respectively. The TTO for one of the reports was 2 days. The age of both females was 30 and 38 years, respectively. Cumulatively, as of 19-Jun-2022, 6 ICSRs of use in pregnancy and while breastfeeding was retrieved, all the reports were non-medically confirmed.

16.3.6.1.3 Conclusion

All the reports of use in pregnancy and use during breastfeeding did not raise any safety concerns. No safety signal was identified.

16.3.6.2 Update on Missing Information Topic: Use in Immunocompromised Patients

NVX-CoV2373 has not been studied in individuals with immunocompromised conditions, except for subjects with HIV.

16.3.6.2.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in immunocompromised patients (refer to Appendix 14).

16.3.6.2.2 Results and Discussion

During the reporting interval and cumulatively, the database query identified 3 ICSRs meeting the prespecified search strategy for use in immunocompromised patients. Cumulatively, as of 19-Jun-2022, 3 ICSRs of use in immunocompromised patients were retrieved. All the reports were non-medically confirmed and involved females; ages ranged from 41-73 years. The 3 ICSRs contained 7 non-medically confirmed AEs including 1 serious and 6 non-serious AEs. Most of the PTs like Herpes zoster (n=1), Peripheral swelling (n=1), Muscle twitching (n=1), Paraesthesia (n=1), Guillain-Barre syndrome (n=1) in these immunocompromised patients were nervous system related. TTO for all 3 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.

16.3.6.2.3 Conclusion

Review of individual reports did not suggest any trends for the AE profile particular to this population compared to the AE profile as defined in the CCDS for the overall population. No safety signal was identified.

16.3.6.3 Update on Missing Information Topic: 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.

16.3.6.3.1 Methodology

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 14).

16.3.6.3.2 Results and Discussion

During the reporting interval and cumulatively, as of 19-Jun-2022, the database query identified 244 ICSRs meeting the prespecified search strategy for use in frail patients with comorbidities. The 244 ICSRs reported a total of 1,224 AEs including 55 serious and 36 non-serious, medically confirmed AEs and 173 serious and 960 non-serious, non-medically confirmed AEs. The most frequently reported PTs were Dizziness (n=35), Chest pain (n=29), Dyspnoea (n=28), Paraesthesia (n=26) and Tachycardia (n=23). Of the 244 ICSRs, 189 were for females (77%), and 54 (22%) for males; the age range was 19-96 years. Most reports were of individuals above

the age of 40 years (n=166, 68%). The outcome of majority of events was reported as not recovered at the time of reporting.

16.3.6.3.3 Conclusion

Review of individual reports did not suggest any trends for the adverse event profile particular to this population compared to the AE profile as defined in the CCDS for the overall population. No safety signal was identified.

16.3.6.4 Update on Missing Information Topic: 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.

16.3.6.4.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for use in patients with autoimmune or inflammatory disorders (refer to Appendix 14).

16.3.6.4.2 Results and Discussion

During the reporting interval and cumulatively, the database query identified 108 ICSRs meeting the prespecified search use in patients with autoimmune or inflammatory disorders. The 108 ICSRs reported a total of 612 AEs including 7 serious and 12 non-serious, medically confirmed AEs; and 103 serious and 490 non-serious, non-medically confirmed AEs. The most frequently reported PTs were Headache (n=39) and Fatigue (n=28). Of the 108 ICSRs, 97 (89%) were for females and 11(10%) for males; the age range was 21-85 years Most reports were of individuals above the age of 40 years (n=71, 65%). The TTO ranged from 0-28 days.

16.3.6.4.3 Conclusion

Review of individual reports did not suggest any trends for the adverse event profile particular to this population compared to the AE profile as defined in the CCDS for the overall population. No safety signal was identified.

16.3.6.5 Update on Missing Information Topic: 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.

16.3.6.5.1 Methodology

The global vaccine safety database was queried for the interval and cumulative ICSRs using the prespecified search strategy for reports of interaction with other vaccines (refer to Appendix 14).

All the reports retrieved based on the search strategy were further filtered manually for vaccines from the non-company co-suspect field and concomitant drugs field for further review and assessment.

16.3.6.5.2 Conclusion

During the reporting interval and cumulatively, no ICSR was retrieved.

16.3.6.6 Update on Missing Information Topic: Long-Term Safety

Understanding of the long-term safety profile of NVX-CoV2373 is currently limited

16.3.6.6.1 Methodology

Long-term safety is evaluated by routine monitoring of Post-Authorisation Safety Studies (PASS).

16.3.6.6.2 Results and Discussion

No patients have been enrolled in the current PASS studies since the authorisation of NVX-CoV2373.

16.3.6.6.3 Conclusion

During the reporting interval and cumulatively, no new information determining long-term safety was identified.

16.4 Characterisation of Risks

Risk characterisation for important potential risks and missing information are discussed in EU RMP Part II, module SVII, based on latest version of EU RMP, V 1.0 that was approved on 20-Dec-2021.

16.5 Effectiveness of Risk Minimisation

Routine risk minimisation measures are in place for NVX-CoV2373; there are no additional risk minimisation measures in place. All signals detected 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

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 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 (2019nCoV-301 adults and 2019nCoV302) and adolescents (2019nCoV-301 adolescents Substudy) are summarised below:

- Overall NVX-CoV2373 prevented PCR-confirmed symptomatic moderate or severe COVID-19 in serologically negative adult and adolescent subjects.
- In adults, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID-19 due to SARS-CoV-2 variant considered or not considered a VOC or VOI with onset from at least 7 days after second vaccination in serologically negative adult subjects.
- In 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.
- In adults, NVX-CoV2373 prevented PCR-confirmed any symptomatic SARS-CoV-2 infection with onset from at least 7 days after second vaccination in serologically negative (to SARS-CoV-2) adult subjects, with results similar to those of the primary efficacy endpoint (VE = 90.55% (95% CI: 83.16, 94.70).
- In adolescents, VE was 79.54% for the primary endpoint and most cases were mild in severity.
- In adolescents, VE was 82.04% due to a SARS-CoV-2 variant considered as a VOC/VOI, which was represented only by the Delta VOC.
- In adolescents, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from at least 7 days after second vaccination in adolescent subjects regardless of baseline serostatus with results similar to those of the primary efficacy endpoint.
- In adolescents, NVX-CoV2373 prevented PCR-confirmed symptomatic mild, moderate, or severe COVID19 with onset from first injection in adolescent subjects regardless of baseline serostatus.

Long term follow-up data are not currently available and safety and efficacy of NVX-CoV2373 has not been studied in pregnant and breastfeeding women, immunocompromised patients (except PLWH) and patients with autoimmune or immunodeficiencies. Post-authorisation studies will further characterise this missing information.

17.2 Newly Identified Information on Efficacy/Effectiveness

During the reporting interval, no new information became available on efficacy or effectiveness that could change the overall benefit risk evaluation of NVX-CoV2373.

17.3 Characterisation of Benefits

Evidence from interim analysis of two pivotal phase III CTs suggested that NVX-CoV2373 was shown to be safe and effective in preventing PCR confirmed COVID-19 infections, when a two-dose series was administered 21 days apart in adults (2019nCoV-301 and 2019nCoV302) and adolescents (2019nCoV-301 adolescents sub study).

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 higher rate of mortality among patients with chronic medical conditions and weakened immune systems. As per World Health Organisation (WHO), more than 539 million confirmed cases of COVID-19 and 6 million deaths have been reported globally since January 2020. Initial observational studies following vaccine rollout suggested that vaccines may lead to protection against COVID-19 infection and also reduce transmission, which in addition to public health and social measures will help control the spread of the virus. Several VOC have emerged since the original Wuhan strain, which are more transmissible and can cause severe disease. There is a public health need to promote equitable access to COVID-19 vaccines, to improve vaccine intake in parts of the world where cold chain technologies are not that established and to provide a traditional option of a protein-based vaccine.

18.2 Benefit-Risk Analysis Evaluation

Based on interim analysis from 2 pivotal phase III CTs, NVX-CoV2373 has demonstrated higher 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 participant 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 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.

Overall, in placebo-controlled phase of clinical development program, the rates of myocarditis and pericarditis were balanced between vaccine and placebo arms at 0.007% for NVX-CoV2373

and 0.005% for placebo. No pericarditis events were reported in pre-cross over phase. In post-crossover phase of studies 2019nCoV-301 and 2019nCOV-302, where all subjects have been exposed to at least one dose of NVX-CoV2373, three events of myocarditis and pericarditis were observed, each with reasonable alternate aetiologies. In post-crossover portion of 301 and 302, where all patients have been exposed to vaccine, events of myocarditis and pericarditis occurred within expected background rates as determined by ACCESS study. There were no events of anaphylaxis reported in CTs. Following the data lock point, NVX recharacterized myocarditis and pericarditis from an important potential risk to an important identified risk. The incidence of myocarditis has been shown to be higher after SARS-CoV-2 infection compared with COVID - 19 vaccination. Moreover, myocarditis after natural viral infection appears to be more severe than myocarditis after COVID-19 vaccination with respect to fulmination, mortality, disease duration, and proportions of cardiac dysfunction and functional recovery [53, 54]. Thus, this update of risk from important potential to important identified risk has no impact on overall benefit-risk balance of NVX-CoV2373.

A summary of important potential risks and missing information are included in Section 16.1. As described in the EU RMP V1.2, there are no important identified risks for NVX-CoV2373. 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.

19 CONCLUSION

Following the data lock point, signal evaluations were completed for AESI of anaphylaxis, myocarditis/pericarditis, and safety topic of paraesthesia/hypoaesthesia. Following DLP, anaphylaxis was added to special warnings and precautions and paraesthesia/hypoaesthesia were added as undesirable side effects in CCDS v5. NVX will be submitting a Type 2 variation for myocarditis/pericarditis along with updates to the core RMP, CCDS and SmPC, in accordance with specified timelines.

The signals of chest pain/chest discomfort, dizziness, encephalitis/encephalomyelitis, have been refuted and SERs have been appended along with this report.

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.