

Nuvaxovid: Periodic safety update report assessment

20 December 2024 to 19 December 2025

This document consists of:

1. The PRAC assessment report of the Nuvaxovid periodic safety update report (PSUR) covering the period 20 December 2024 to 19 December 2025, and;
2. The Nuvaxovid PSUR itself.

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

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

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

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

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

Further information on the [safety of COVID-19 vaccines](#) and on [PSUR submission and assessment](#) is available on the EMA website.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMADOC-1700519818-2991838
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000336124

PRAC PSUR assessment report

EURD list no.: PSUSA/00010972/202512

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

Period covered by the PSUR: 1 year to 19 December 2025

Centrally authorised Medicinal product(s): For presentations: See Annex A	Marketing Authorisation Holder
Nuvaxovid	Sanofi Winthrop Industrie



Status of this report and steps taken for the assessment			
Current step	Description	Planned date	Actual Date
☐	Start date	12 March 2026	12 March 2026
☐	PRAC Rapporteur AR	11 May 2026	11 May 2026
☐	PRAC/MAH comments	10 June 2026	10 June 2026
☐	Updated PRAC Rapporteur AR	25 June 2026	22 June 2026
☒	PRAC outcome	9 July 2026	9 July 2026

Procedure resources	
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1. Background information on the procedure

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

2. Assessment conclusions and actions

This assessment report refers to the 7th periodic benefit-risk evaluation report (PBRER)/periodic safety update report (PSUR) for Nuvaxovid, Nuvaxovid XBB.1.5, Nuvaxovid JN.1 and Nuvaxovid LP.8.1, Coronavirus disease 2019 (COVID-19) vaccine (recombinant, adjuvanted), dispersion for injection. The active substance is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda*, with the international birth date (IBD) 20 December 2021. Nuvaxovid XBB.1.5, which is Nuvaxovid updated for the SARS-CoV-2 Omicron XBB.1.5 subvariant, has been authorised in the European Union (EU) on 31 October 2023. The updated vaccine for the Omicron JN.1 subvariant, Nuvaxovid JN.1, has been authorised in the EU on 08 October 2024. During the period covered by the report, a MA for Nuvaxovid LP.8.1 was granted in Japan on 27 August 2025. To date, Nuvaxovid LP.8.1 is not approved in any other country. This PSUR covers the one year interval between 20-Dec-2024 to 19-Dec-2025.

All SARS-CoV-2 recombinant spike (rS) nanoparticle vaccines contain purified rS protein antigens stabilised in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against COVID-19. In the EU, the vaccines (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) are indicated for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

According to the MAH, clinical trial exposure comprises a cumulative total of 58 665 participants exposed to at least one dose of SARS-CoV-2 recombinant, adjuvanted vaccines, either monovalent or bivalent, prototype or variant. A total of 6,459 participants were engaged in blinded treatment arms of studies across the MAH-sponsored SARS-CoV-2 rS and COVID-19 influenza combination clinical development programs. An additional 1,422 participants were exposed to the prototype SARS-CoV-2 rS vaccine in two MAH-sponsored clinical trials involving a COVID-19 influenza combination vaccine. Post authorisation, the overall Nuvaxovid (any strain) vaccine doses distributed cumulatively since launch is estimated to be 128 333 910 and the Nuvaxovid JN.1-vaccine doses distributed during the interval period is estimated to be 2 567 000.

No new signals were validated, ongoing or closed during the reporting interval.

During the reporting interval, the MAH did not identify any new important risks or any new significant information related to existing risks.

No actions were taken during the reporting interval for safety reasons related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), Regulatory Authorities, data monitoring committees, or ethics committees that had (i) significant influence on the risk-benefit profile of the approved medicinal product; and/or (ii) an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

The company core data sheet (CCDS) for COVID-19 vaccine, version 10 dated 30 May 2024 was the reference safety information (RSI) valid at the beginning of the PBRER period. During the reporting

period the RSI was revised twice. On 4 February 2025, the adverse reactions section was updated to update the percentages of the most frequently reported adverse reactions in adults following a booster dose, based on data from final clinical study report (CSR) from studies 2019nCoV 101 Part 2, 2019nCoV-301 and 2019nCoV-311 Part 1 (CCDS version 11). On 11 June 2025, the adverse reactions section was revised with a view to updating the incidence percentages of the most frequently reported adverse reactions based on data from studies 2019nCoV-301 (adolescents and adults populations) and 2019nCoV-311 Part 2 (adults' populations). In addition, the clinical efficacy section was also updated to revise final efficacy and immunogenicity in adolescents and adults, based on study 2019nCoV 301 (CCDS version 12,). The current RSI at the data lock point (DLP) is CCDS version 12, dated 11 June 2025.

There were no changes to the list of safety concerns. In the EU, myocarditis and/or pericarditis is an important identified risk; vaccine associated enhanced disease, including vaccine-associated enhanced respiratory disease, is an important potential risk. Missing information includes the use in pregnancy and while breastfeeding, the use in immunocompromised patients, the use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders), the use in patients with autoimmune or inflammatory disorders, the interaction with other vaccines, and long-term safety. During the reporting interval, the MAH did not identify relevant new information related to these safety concerns.

Following recent publications on the association between cancer and COVID-19 vaccination, the MAH is requested to submit in the next PSUR, a review of the published literature on the potential relationship between COVID-19 vaccination and increased risk of cancer and cancer hospitalisations and provide a discussion on the most relevant strengths and limitations of the available data.

To conclude, the safety profile of Nuvaxovid, Nuvaxovid XBB.1.5, Nuvaxovid JN.1 and Nuvaxovid LP.8.1 remains within the expected scope. The data provided by the MAH does not alter previous assessments of efficacy or effectiveness.

Based on the assessment of the data presented in this PSUR, the benefit-risk balance of SARS-CoV-2, spike protein, recombinant, expressed in sf9 cells derived from *spodoptera frugiperda* (Nuvaxovid, Nuvaxovid XBB.1.5, Nuvaxovid JN.1, Nuvaxovid LP.8.1) remains unchanged in its authorised indications.

3. Recommendations

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

4. Issues to be addressed in the next PSUR

In view of the below recent publications on increased risk of cancer and/or cancer hospitalisation following a COVID-19 vaccine, the MAH should submit in the next PSUR, a review of the published literature (including but not limited to the below publications) on the potential relationship between COVID-19 vaccination and increased risk of cancer and cancer hospitalisations and provide a discussion on the most relevant strengths and limitations of the available data.

- Martellucci, C. A., Capodici, A., Soldato, G., Fiore, M., Zauli, E., Carota, R., ... & Manzoli, L. (2025). COVID-19 vaccination, all-cause mortality, and hospitalization for cancer: 30-month cohort study in an Italian province. *EXCLI journal*, 24, 690.
- Kim, H. J., Kim, M. H., Choi, M. G., & Chun, E. M. (2025). 1-year risks of cancers associated with COVID-19 vaccination: a large population-based cohort study in South Korea. *Biomarker Research*, 13(1), 114.

5. PSUR frequency

☒ No changes to the PSUR frequency

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

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This periodic safety update report (PSUR) for Nuvaxovid, Nuvaxovid XBB.1.5, Nuvaxovid JN.1 and Nuvaxovid LP.8.1 covers the 1 year interval between 20 December 2024 and 19 December 2025. The vaccine's international birth date (IBD), as well as the European Union (EU) reference date (EURD), is 20 December 2021. The COVID-19 vaccine belongs to the therapeutic class of COVID-19, protein subunit.

Currently three of these vaccines are authorised in the EU under the trade names Nuvaxovid (NVX-CoV2373), Nuvaxovid XBB.1.5 (NVX-CoV2601) and Nuvaxovid JN.1 (NVX-CoV2705).

All SARS-CoV-2 recombinant spike (rS) nanoparticle vaccines contain purified rS protein antigens stabilised in the pre-fusion conformation, plus the saponin-based Matrix-M adjuvant which facilitates activation of the cells of the innate immune system and enhances the magnitude of the rS protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the rS protein antigen, including neutralising antibodies, which may contribute to protection against Coronavirus disease 2019 (COVID-19). The vaccines are administered intramuscularly and indicated for the active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

The COVID-19 vaccine is available as colorless to slightly yellow and clear to mildly opalescent dispersion for injection. It is available as one single-dose vial which contains one dose of 0.5 mL, one multidose vial which contains five or 10 doses of 0.5 mL per vial, and one single-dose pre-filled syringe which contains one dose of 0.5 mL. One dose (0.5 mL) contains: 5 micrograms of the SARS-CoV-2rS and is adjuvanted with Matrix-M.

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

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

1.2. Worldwide marketing authorisation status

According to PSUR Appendix 5.1.2, Nuvaxovid was first authorised in Indonesia on 31 October 2021 (Covovax). Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 were first authorised in the United States (US) on 03 October 2023 (Novavax COVID-19 vaccine, adjuvanted [2023-2024 formula]; and on 30 August 2024 (Novavax COVID-19 vaccine, adjuvanted [2024-2025 formula]), respectively. Nuvaxovid LP.8.1 was first (and only) authorised in Japan on the 27-Aug-2025. In the EU, Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 were authorised on 20 December 2021, 31 October 2023 and 08 October 2024, respectively.

Nuvaxovid:

The first marketing authorization (MA) for Nuvaxovid was obtained in the European Union (EU) on 20 December 2021. Nuvaxovid received marketing authorisation or emergency use authorisation as a two dose primary series and as a booster for individuals 12 years and older in several countries, the EU region and by the World Health Organisation (WHO), under the trade names Nuvaxovid, Covovax, and

as Novavax COVID-19 vaccine, adjuvanted, in the US. Nuvaxovid is approved in 48 countries worldwide (including Sanofi and Partner territories). In India, Covovax is authorised as a two-dose primary series in individuals 7 years of age and older and as a booster for individuals 18 years of age and older. In Japan, Nuvaxovid is authorised as a two-dose primary series in individuals 6 years of age and older, and as a booster in individuals 12 years of age and older. In Switzerland, the approval of Nuvaxovid was withdrawn on 21 March 2024.

During the period covered by this report, a MA for Nuvaxovid was granted in the United States (US) on 16 May 2025 and in Israel on 10 August 2025. Nuvaxovid is prequalified by the World Health Organization (WHO) since 20 December 2021 as part of the Emergency use listing (EUL).

Table 1: Worldwide Marketing Authorization Status for Nuvaxovid– invented names and countries/region of authorisation (adapted from PSUR Appendix 5.1.2, Table 1, pp. 325-328)

Nuvaxovid	Australia, Canada, EU, Israel, Japan, New Zealand, Singapore, South Korea, Taiwan, United Arab Emirates, United Kingdom, World Health Organisation
Novavax COVID-19 Vaccine, Adjuvanted	United States
Covovax	Bangladesh, Brazil, India, Indonesia, Philippines, South Africa, Thailand, World Health Organisation

Nuvaxovid XBB.1.5:

The first MA for Nuvaxovid XBB.1.5 was obtained in the US on 03 October 2023. Nuvaxovid XBB.1.5 is approved in 38 countries worldwide (including Sanofi and Partner territories).

During the period covered by the report, Nuvaxovid XBB.1.5 did not receive additional MA.

Nuvaxovid XBB.1.5 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) regardless of previous vaccination status.
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

The alternative name for Nuvaxovid XBB.1.5 is Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula) in Brazil and India and Novavax COVID-19 Vaccine, Adjuvanted 2023-2024 formula in PFS, in South Korea.

Nuvaxovid XBB.1.5 is prequalified by the WHO since 22 November 2023 as part of the EUL.

Table 2: Worldwide Marketing Authorization Status for Nuvaxovid XBB.1.5– invented names and countries/region of authorisation (adapted from PSUR Appendix 5.1.2, Table 2, pp. 329-330)

Covovax COVID-19 vaccine adjuvanted (2023-2024 formula)	Brazil, India
Novavax COVID-19 vaccine 2023-2024 formula in PFS	South Korea

Nuvaxovid XBB.1.5	Canada, EU, Singapore, Taiwan, UK, WHO
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Nuvaxovid JN.1:

The first MA for Nuvaxovid JN.1 was obtained in the US on 30 August 2024. Nuvaxovid JN.1 is approved in 37 countries worldwide (including Sanofi and Partner territories).

During the period covered by the report, a MA for Nuvaxovid JN.1 was granted in three countries, including the US on 16 May 2025 (2024-2025 Formula) and 27 August 2025 (2025-2026 Formula), Taiwan on 26 May 2025 and in the United Kingdom (UK) on 29 August 2025.

During the period covered by the report, the Emergency Use Authorization (EUA) was withdrawn in the US on 27 August 2025 (EUA 28237), following the above-mentioned BLA approval.

Nuvaxovid JN.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status..
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In the US, Nuvaxovid JN.1 (Nuvaxovid COVID-19 Vaccine, Adjuvanted [2025-2026 Formula]) is approved for use in individuals who are:

- 65 years of age and older, or
- 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In South Korea, and the US the alternative name for Nuvaxovid JN.1 is Novavax COVID-19 Vaccine 2024-2025 formula. Nuvaxovid JN.1 is prequalified by the WHO since 26 June 2025.

Table 3: Worldwide Marketing Authorization Status for Nuvaxovid JN.1: – invented names and countries/region of authorisation (adapted from PSUR Appendix 5.1.2, Table 3, p. 331-333).

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

Nuvaxovid LP.8.1:

The first MA for Nuvaxovid LP.8.1 was obtained in Japan and is part of a licensing agreement between Novavax and Takeda.

Nuvaxovid LP.8.1 is only approved in one country (Japan) worldwide.

During the period covered by the report, a MA for Nuvaxovid LP.8.1 was granted in Japan on 27 August 2025.

Nuvaxovid LP.8.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 as

an initial immunization (first and second vaccination) for those aged six years or older and a booster immunization (after the third vaccination) for those aged 12 years or older.

Table: Worldwide Marketing Authorization Status for Nuvaxovid LP.8.1 – invented names and country/region of authorisation (adapted from PSUR Appendix 5.1.2, Table 4, p. 334).

NUVAXOVID	Japan
Intramuscular Injection 1 mL (Recombinant Coronavirus (SARS-CoV-2) Vaccine, Omicron JN.1) (2 dose vials)	

Rapporteur assessment comment:

During the period covered by this report, a MA for Nuvaxovid was granted in the United States (US) on 16 May 2025 and in Israel on 10 August 2025, Nuvaxovid XBB.1.5 did not receive additional MA, a MA for Nuvaxovid JN.1 was granted in three countries, including the US on 16 May 2025 (2024-2025 Formula) and 27 August 2025 (2025-2026 Formula), Taiwan on 26 May 2025 and in the United Kingdom (UK) on 29 August 2025, whereby the Emergency Use Authorization (EUA) was withdrawn in the US on 27 August 2025 (EUA 28237). Moreover, during the period covered by the report, a MA for Nuvaxovid LP.8.1 was granted in Japan on 27 August 2025. Nuvaxovid LP.8.1 is only approved in one country (Japan) worldwide.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

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

- A significant influence on the risk-benefit profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

1.3.2. Changes to reference safety information

The company core data sheet (CCDS) for COVID 19 vaccine, version 10 dated 30 May 2024 was the reference safety information (RSI) valid at the beginning of the PBRER period.

The RSI was revised to:

The CCDS version 11, dated 04 February 2025, and the following amendments were made:

Adverse reactions section

- o Updated the incidence percentages of most frequently reported adverse reactions in adults following a booster dose, based on data from final clinical study report (CSR) from studies 2019nCoV 101 Part 2, 2019nCoV-301 and 2019nCoV-311 Part 1.
- o Editorial updates throughout the section.

The CCDS version 12, dated 11 June 2025, and the following amendments were made:

Adverse reactions section was revised to:

- o Update the incidence percentages of most frequently reported adverse reactions based on data from studies 2019nCoV-301 (adolescents and adults populations) and 2019nCoV-311 Part 2 (adults populations).

Clinical Efficacy section was updated to:

- o Revise final efficacy and immunogenicity, based on final data from Study 2019nCoV 301 in adolescents aged 12 to 17 years.
- o Revise immunogenicity data following booster dose administration in adults, as per final data from Study 2019nCoV-301.
- o Revise the number of participants from Study 2019nCoV-311, Part 2.

The current RSI at the data lock point (DLP) is the CCDS version 12, dated 11 June 2025.

Rapporteur assessment comment:

CCDs was updated twice during the reporting period to include most recent clinical trial data, this is considered acceptable. The current RSI at the data lock point (DLP) is the CCDS version 12, dated 11 June 2025. Based on the information provided in this PSUR, the MAH does not make any proposals in terms of new safety information and key risk minimisation recommendations.

1.3.3. Estimated exposure and use patterns

Clinical trial exposure

According to the MAH, clinical trial exposure comprises a cumulative total of 58,665 participants exposed to at least one dose of SARS-CoV-2 vaccines, either monovalent or bivalent, prototype or variant, or blinded treatment. A total of 6,459 participants were engaged in blinded treatment arms of studies across the MAH-sponsored SARS-CoV-2rS and COVID-19 influenza combination clinical development programs. An additional 1,422 participants were exposed to the prototype SARS-CoV-2 rS vaccine in two MAH-sponsored clinical trials involving a COVID-19 influenza combination vaccine.

The MAH's COVID-19 vaccines include the monovalent vaccines prototype (NVX-CoV2373; n = 46,776 participants exposed in clinical trials), BA.1 (NVX-CoV2515; n = 347), BA.5 (NVX-CoV2540; n = 297), XBB.1.5 (NVX-CoV2601; n = 1,671), and JN.1 (NVX-CoV2705; n = 955); the bivalent vaccines prototype + BA.1 (NVX-CoV2373 + NVX-CoV2515; n = 269), prototype + BA.5 (NVX-CoV2373 + NVX-CoV2540; n = 259) and prototype + XBB.1.5 (NVX-CoV2373 + NVX-CoV2601; n = 210); and the COVID-19 and influenza combination (CIC) vaccines prototype (NVX-CoV2373) + quadrivalent nanoparticle influenza vaccine (n = 1,422) and JN.1 (NVX-CoV2705) + trivalent nanoparticle influenza vaccine (n = 1,985 participants who received blinded treatment). A total of 6,459 participants were exposed to blinded treatment, and 8,460 subjects were exposed to placebo. The MAH presents cumulative exposure data by age and gender (PSUR Tables 2 and 3, p. 25-26) and by racial group (PSUR Table 4, p. 26-27). A total of 2,595 individuals from 12 to < 18 years of age were exposed to the vaccines. Participants under 12 years of age received blinded treatment only (6 to < 24 months, n = 1,164; 2 to < 6 years, n = 1,216; 6 to < 12 years, n = 1,260). A total of 8,621 subjects > 65 years received the COVID-19 vaccines or blinded treatment.

Table 4: Cumulative Participant Exposure by Clinical Trial and Study Treatment

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-101 Part 1	23	–	–	–	108	–	–	–	–	–	–	108
2019nCoV-101 Part 2	254	–	–	–	1029	–	–	–	–	–	–	1029
2019nCoV-205	–	–	–	–	91	–	–	811	–	–	–	902 ^b
2019nCoV-301 Adult	3458	–	–	–	26 124	–	–	–	–	–	–	26 124
2019nCoV-301 Peds	75	–	–	–	2157	–	–	–	–	–	–	2157
2019nCoV-302	4346	–	–	–	10 792	–	–	–	–	–	–	10 792
2019nCoV-307	–	–	–	–	905	–	–	–	–	–	–	905
2019nCoV-311 Part 1	–	347	–	–	335	269	–	–	–	–	–	951
2019nCoV-311 Part 2	–	–	254	–	251	–	259	–	–	–	–	764
2019nCoV-312	–	–	43	–	104	–	–	–	–	–	–	147

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XB B.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-313 Part 1	—	—	—	—	—	—	—	332	—	—	—	332
2019nCoV-313 Part 2	—	—	—	—	—	—	—	338	—	—	—	338
2019nCoV-314	—	—	—	—	—	—	—	190	210	—	—	400
2019nCoV-315	—	—	—	—	—	—	—	—	—	60	—	60
2019nCoV-318	—	—	—	—	—	—	—	—	—	676	—	676
2019nCoV-501	304	—	—	—	4104	—	—	—	—	—	—	4104
2019nCoV-415	—	—	—	—	—	—	—	—	—	219	—	219
2019nCoV-420	—	—	—	—	—	—	—	—	—	—	834	834
2019nCoV-503	—	—	—	—	—	—	—	—	—	—	3640	3640 ^c
2019nCoV-505	—	—	—	—	383	—	—	—	—	—	—	383
2019nCoV-ICC-E-101 ^a	—	—	—	558	78	—	—	—	—	—	—	636

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XB B.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-CIC-E-201 ^a	—	—	—	864	315	—	—	—	—	—	—	1179
CIC-E-301 ^a	—	—	—	—	—	—	—	—	—	—	1985	1985
Total	8460	347	297	1422	46776	269	259	1671	210	955	6459	58 665^d

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

^b Ninety-one (91) participants who took mRNA were excluded from the 2019nCoV-205 study total.

^c For Study 503, some participants were identified for cross-enrolment in different sites. For example, the same participant could have three different subject IDs when the participant enrolled in the study from three different sites. In the current statistical programming, unique participants were counted instead of counting all subject IDs. Therefore, the number of participants in Study 503 in the current tables is less than the PBRER No.05 (20-Dec-2023 to 19-Jun-2024) table which counted all subject IDs.

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

CIC: COVID-19 Influenza Combination Nanoparticle Vaccine; mRNA: messenger Ribonucleic acid; PBRER: Periodic Benefit Risk Evaluation Report.

Rapporteur assessment comment:

According to PSUR Table 1, a total of 58,665 participants (147 participants from 2019nCoV-312 study counted twice; 220 participants from 2019nCoV-415 study excluded) were exposed to at least one dose of Novavax COVID-19 vaccines or blinded treatment. According to the data provided, predominantly adults were included in clinical trials with the vaccines (18-65 years, n = 43,590, including participants exposed to blinded treatment and subjects from study 2019nCoV-312 counted twice, excluding participants from 2019nCoV-415 study). The sex distribution of the participants is quite balanced (male=29,829 vs. female 28,830), and the majority of subjects are described as White or Caucasian (n = 41,269).

Post-authorisation exposure

Post-approval (non-clinical trial) exposure

Interval sales

The total doses distributed during the interval period for Nuvaxovid JN.1 is 2 567 000. No doses were distributed for Nuvaxovid and Nuvaxovid XBB.1.5 during the interval period.

Cumulative sales

The total doses distributed during the cumulative period for Nuvaxovid is 104 284 800, for Nuvaxovid XBB.1.5 is 18 134 270, and for Nuvaxovid JN.1 is 5 914 840.

Overall doses distributed (Sanofi and Partner Novavax)

Based on the sales figure available from Sanofi and partner Novavax, the overall COVID-19 vaccine doses distributed during the cumulative period is estimated to be 128 333 910 and the overall COVID-19 vaccine doses distributed during the interval period is estimated to be 2 567 000.

Table 5: Interval Exposure from Marketing Experience - NOVAVAX INC COVID-19 VACCINE (RECOMBINANT, ADJUVANTED)-20 December 2024 to 19 December 2025; PSUR Appendix 5.2.1, p. 336

COUNTRY	Nuvaxovid JN.1
GERMANY	93 060
ISRAEL	99 680
MOROCCO	320 510
SINGAPORE	145 050
SWEDEN	7200
TAIWAN	225 360
UNITED STATES OF AMERICA	1 676 140
Total doses	2 567 000

Units: Number of doses distributed

Of note: The distribution data provided includes all distribution since the International Birth Date (20 December 2021) till 19 December 2025. The first Novavax commercial shipment was in February 2022, and there have been no additional shipments since November 2025.

Table 6: Cumulative Exposure from Marketing Experience - NOVAVAX INC 20 December 2021 to 19 December 2025 COVID-19 VACCINE (RECOMBINANT, ADJUVANTED); PSUR Appendix 5.2.2, p. 338

COUNTRY	Nuvaxovid	Nuvaxovid XBB.1.5	Nuvaxovid JN.1
AUSTRALIA	27 384 800	0	0
AUSTRIA	3 192 000	175 000	0
BELGIUM	443 000	0	0
CANADA	9 749 000	125 000	0
CROATIA	165 000	0	0
CYPRUS	42 200	9800	0
CZECH REPUBLIC	572 000	200 000	0
DENMARK	608 000	372 000	0
ESTONIA	80 800	0	0
FINLAND	417 000	165 000	0
FRANCE	2 995 000	100 000	0
GERMANY	27 504 900	9 385 510	458 060
GREECE	406 000	0	0
ICELAND	45 000	0	0
IRAN	0	271 000	0
IRELAND	479 000	0	0
ISRAEL	2 000 000	0	99 680
ITALY	3 972 000	2 932 200	0
LATVIA	225 000	126 400	0
LITHUANIA	288 000	177 000	0
LUZEMBOURG	105 000	0	0
MALTA	21 000	0	0
MOROCCO	0	0	320 510
NETHERLANDS	707 000	3000	0
NEW ZEALAND	3 288 000	0	0
NICARAGUA	27 500	0	0
NORWAY	642 000	0	0
POLANDS	5 475 000	823 000	0
PORTUGAL	408 000	0	0
SINGAPORE	705 000	50 200	244 800
SLOVAKIA	434 000	213 500	0
SLOVENIA	144 000	40 000	0
SOUTH KOREA	0	504 000	319 900
SPAIN	1 889 900	1580	0
SWEDEN	1 870 000	280 000	7200
SWITZERLAND	526 400	0	0
TAIWAN	1 805 200	627 800	425 360
UNITED KINGDOM	972 500	8070	0
UNITED STATES OF AMERICA	4 737 800	1 544 210	4 039 330
Total	104 284 800	18 134 270	5 914 840
Cumulative Total doses	128 333 910		

Units: Number of doses distributed

Of note: The distribution data provided includes all distribution since the International Birth Date (20 December 2021) till 19 December 2025. The first Novavax commercial shipment was in February 2022, and there have been no additional shipments since November 2025.

Post-approval use in special populations

The MAH does not have access to cumulative exposure regarding use in special populations from the IBD of COVID-19 vaccine through the DLP of the PBRER.

Other post-approval use

The MAH stated, that no patterns of use with COVID-19 vaccine beyond that recommended in the reference product information, including overdose, drug abuse and misuse considered relevant for the interpretation of safety data were identified.

Rapporteur assessment comment:

According to Appendix 5.2.1 (PSUR p. 336), a total of 2 567 000 and doses of NOVAVAX INC COVID-19 VACCINE (RECOMBINANT, ADJUVANTED) are estimated to have been administered during the reporting interval.

Cumulatively 128 333 910 doses of NOVAVAX INC COVID-19 VACCINE (RECOMBINANT, ADJUVANTED) (Nuvaxovid, 104 284 800 doses; Nuvaxovid XBB.1.5, 18 134 270 doses; Nuvaxovid JN.1, 5 914 840 doses) are estimated to have been administered (Appendix 5.2.2(PSUR p. 338)). The MAH stated, that there was no Sanofi sales data retrieved for the cumulative period (20 December 2021 to 19 December 2025) as well as for the interval period (20 December 2024 to 19 December 2025).

1.3.4. Data in summary tabulations

The Medical Dictionary for Regulatory Activities (MedDRA) version 28.1 was used for the coding of serious adverse events (SAEs) and adverse drug reactions (ADRs).

Cumulative summary tabulations of serious adverse events from clinical trials

In PSUR Appendix 2.1 (p. 120 -168), the MAH provides the cumulative tabulation of serious adverse events (SAEs) reported from MAH-sponsored, interventional clinical trials where COVID-19 vaccine was the product under investigation from the development international birth date (DIBD) 23 April 2020 to the DLP (19 December 2025) of the periodic benefit-risk evaluation report (PBRER). The cumulative SAE tabulation is presented by treatment arm for completed or unblinded trials and blinded for ongoing blinded trials. The MAH stated, that a total of 2987 cumulative SAEs were reported from MAH-sponsored clinical trials.

The most frequent reported AEs fall under MedDRA system organ classes (SOCs) Infections and infestations (n=726 AEs; preferred term [PT] Pneumonia, n=101 and PT COVID-19, n=91), Cardiac disorders (n=315; PT Atrial fibrillation, n= 54)and Injury, poisoning and procedural complications (n=272).

Cumulative and interval summary tabulations from post-authorisation data

Interval and cumulative counts of serious and non-serious adverse reactions for spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and Regulatory Authorities; Serious adverse reactions from non-interventional studies and solicited reports of serious adverse reactions are provided in Appendix 2.2.

Appendix 2.2.1 includes the cumulative and interval summary tabulation of serious and non-serious adverse reactions from marketed experience for COVID-19 vaccine (PSUR pp. 169-253) and Appendix 2.2.2 includes the cumulative and interval summary tabulation of serious and non-serious adverse reactions from marketed experience for unknown manufacturer COVID-19 vaccines (PSUR pp. 254-267).

A total of 21 792 cumulative adverse reactions have been reported for COVID-19 vaccine, 1824 of which were reported during the present reporting period (see Appendix 2.2.1). The most frequently reported AEs fall under MedDRA system organ classes (SOCs) General disorders and administration site conditions (n=6,321 AEs; PT Fatigue n=784, PT Pyrexia n= 678, PT Chest pain n=548, PT

Injection site pain=512), Nervous system disorders (n=3,551 AEs; PT Headache n= 1158, PT Dizziness n=657), Musculoskeletal and connective tissue disorders (n= 2,360 AEs; Myalgia n=722, PT Pain in extremity n=477), Gastrointestinal disorders (n=1,387; PT Nausea n=526, PT Vomiting n=178, PT Diarrhoea n=156) and Skin and subcutaneous tissue disorders (n=1,230 AEs; PT Rash n=329).

A total of 254 cumulative adverse reactions have been reported for unknown manufacturer COVID-19 vaccines, of which 51 were reported during the present reporting period (see Appendix 2.2.2). The most frequently reported AEs fall under MedDRA SOCs General disorders and administration site conditions (n=69 AEs; PT Pyrexia n=11), Nervous system disorders (n=35 AEs; PT Headache n=10), Respiratory, thoracic and mediastinal disorders (n=26 AEs) and Musculoskeletal and connective tissue disorders (n=25 AEs).

Rapporteur assessment comment:

The MAH stated, that a total of 2987 cumulative SAEs were reported from MAH-sponsored clinical trials.

A total of 21 792 cumulative adverse reactions have been reported for COVID-19 vaccine, 1824 of which were reported during the present reporting period. The most frequently reported AEs fall under MedDRA system organ classes (SOCs) General disorders and administration site conditions (n=6,321 AEs), Nervous system disorders (n=3,551 AEs), Musculoskeletal and connective tissue disorders (n= 2,360 AEs), Gastrointestinal disorders (n=1,387) and Skin and subcutaneous tissue disorders (n=1,230 AEs).

A total of 254 cumulative adverse reactions have been reported for unknown manufacturer COVID-19 vaccines, of which 51 were reported during the present reporting period.

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

1.3.5. Findings from clinical trials and other sources

Completed clinical trials

As of the DLP for this PBRER (19 December 2025), the following clinical trial was completed (ie, a final CSR was approved): Study 2019nCoV-315 safety and immunogenicity of an Omicron JN.1 subvariant vaccine (A Phase 3 open-label, single arm study to evaluate the safety and immunogenicity of a JN.1 subvariant SARS-CoV-2rS vaccine). The MAH stated, that no new clinically important safety or efficacy information emerged from this trial during the reporting interval.

The following clinical trial concluded (ie, a final CSR was approved) during the previous reporting period but was erroneously considered and reported as ongoing: Study 2019nCoV-205 High Dose SARS-CoV-2rS Vaccines Booster (A Phase 2/3, Randomized, Double- Blind- Study to Evaluate the Safety and Immunogenicity of Different Booster Dose Levels of Monovalent SARSCoV- 2 rS Vaccines in Adults ≥ 50 Years Previously Vaccinated with COVID-19 mRNA Vaccines). The MAH noted, that no new clinically important safety or efficacy information emerged from this trial during either the previous or current reporting interval.

Ongoing clinical trials

As of the DLP for this PBRER (19 December 2025), the following clinical trials were ongoing (ie, final CSRs were not prepared): Study 2019nCoV-503, Study 2019nCoV-318 (Sanofi VB23344), Study 2019nCoV-420, and Study 2019nCoV-415. The MAH stated, that during the PBRER reporting interval, no interim analyses were planned or conducted for any of the ongoing clinical trials and that, there was no new clinically important information arising from studies ongoing during the reporting interval.

The following studies were ongoing during the reporting interval:

Study 2019nCoV-503 is a phase 2/3 age de-escalating study to evaluate the safety and immunogenicity of SARS-CoV-2 rS protein vaccine with Matrix-M adjuvant in children 6 months to < 12 years of age.

Study 2019nCoV-318 is a Phase 3 Open- Label, Single-Arm Study to Evaluate the Safety and Immunogenicity of an Omicron JN.1 Subvariant SARSCoV- 2 rS Vaccine Adjuvanted with Matrix-M

Study 2019nCoV-420 is a Phase 4, Randomized, Double-Blind, Placebo-Controlled, Post-Marketing Study to Evaluate the Efficacy and Safety of an Omicron JN.1 Subvariant SARSCoV- 2 rS Vaccine Adjuvanted with Matrix-M in Adults 50 to < 65 Years of Age Without High-Risk Conditions for Severe COVID-19

Study 2019nCoV-415 is a prospective interventional study conducted at the University of Utah Health to assess the impact of reactogenicity among healthcare workers and first responders receiving an updated 2024-25 Novavax COVID-19 vaccine (NVX-CoV2705) as compared with those receiving a 2024-25 Pfizer-BioNTech mRNA COVID-19 vaccine in a real-world setting in the US.).

Long-term follow-up

According to the MAH, there were no long-term follow-up programs or studies during the reporting interval.

Other therapeutic use of medicinal product and new safety data related to fixed combination therapies

The MAH notes that no expanded access programs, compassionate use programs, particular patient use, single patient Investigational New Drugs (INDs) or treatment INDs were ongoing or completed during the reporting interval and that the development program does not include a fixed combination product or a multi-drug regimen.

Non-interventional studies

During the reporting interval, three Post-Authorization Safety Studies (PASS) and three Post-Authorization Efficacy Studies (PAES) were ongoing. No MAH-sponsored non-interventional studies were completed during the reporting interval. There was also one collaborative research PAES study (BEEHIVE) ongoing during the reporting interval.

According to the MAH, there were no safety or efficacy findings relevant to the benefit-risk assessment identified from non-interventional studies during the reporting interval.

Other clinical trial/study sources

OTHER CLINICAL TRIALS

According to the MAH, no other clinical trial/study were ongoing or completed during the reporting period.

MEDICATION ERRORS

A total of 52 cases were associated with medication errors during the reporting interval.

Cases with Nuvaxovid:

The MAH retrieved a total of eight cases of medication error for the reporting interval out of which three cases were serious and five cases were non-serious. These cases included eight AEs related to medication error which were coded to PTs: *Accidental overdose* (n = 3), *Incorrect dose administered*

(n = 1), *Interchange of vaccine products* (n = 1), *Incomplete course of vaccination* (n = 1), *Incorrect route of product administration* (n = 1) and *Inappropriate schedule of product administration* (n = 1). In serious cases, the reported AEs were not related to medication error. In non-serious cases, no AEs were reported following medication error.

Cases with Nuvaxovid XBB.1.5:

A total of two cases of medication error were reported during the review period out of which one case was serious and one case was non-serious. These cases included two AEs related to medication error which were coded to PT: *Incomplete course of vaccination* (n = 2). In these cases, the reported AEs were not related to medication error.

Cases with Nuvaxovid JN.1:

A total of 40 cases of medication error were reported during the review period out of which one case was serious and 39 cases were non-serious. These cases included 41 AEs related to medication error which were coded to PTs: *Expired product administered* (n = 16), *Incorrect route of product administration* (n = 8), *Incomplete course of vaccination* (n = 7), *Incorrect dose administered* (n = 2), *Circumstance or information capable of leading to medication error* (n = 1), *Intercepted product storage error* (n = 1), *Needle issue* (n = 1), *Product administered at inappropriate site* (n = 1), *Product administered to patient of inappropriate age* (n = 1), *Product administration error* (n = 1), *Product dose omission issue* (n = 1) and *Product use issue* (n = 1). In one serious case, the patient experienced pain and tendon injury as the tendon had been injected through during vaccination resulting in a hole. The event was managed through surgery. In 35 non-serious cases, no AEs were reported following medication error. In the remaining four cases, the reported AEs were not related to medication error.

Unknown manufacturer COVID-19 vaccines:

A total of two non-serious cases of medication error were reported during the review period. These cases included two AEs related to medication error which were coded to PT: *Extra dose administered* (n = 1) and *Accidental exposure to product* (n = 1). In one case, the reported AEs were not related to medication error while in another case, no AEs were reported following medication error.

The MAH stated, that there were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMMs) at this time. The information on patterns of medication errors and potential medication errors does not change the overall benefit-risk evaluation of COVID-19 vaccine.

No published significant safety findings regarding medication errors have been available during the reporting interval.

Non-clinical data

No significant findings have been identified during the reporting interval.

Literature

During the reporting period, one publication containing new and significant safety findings was identified in the scientific (including non-clinical) and medical literature.

Mackenzie LJ, Bousie JA, Newman P, Cunningham J, Woodward AP, Silk-Jones J, et al. What three years of COVID-19 vaccine administration reveals about the incidence of shoulder injury related to vaccine administration (SIRVA). *Vaccine*. 2025 Apr 2;51:126892. (1)

Background

Shoulder injury related to vaccine administration (SIRVA) has been reported to be a rare but real complication of vaccination. It is considered attributable to an incorrect vaccine administration technique by the vaccinator. To date, evidence about SIRVA is mainly limited to case studies and case series, and the incidence remains unknown. This study aimed to determine the incidence of SIRVA.

Methods

The authors conducted a retrospective study of the publicly available Eudravigilance database (PV data). The authors examined all COVID-19 vaccine case reports administered between January 2020 and December 2022. The reports were analyzed to see if they met the Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) definition and inclusion criteria for SIRVA.

Results

Between January 2020, and December 2022, from 1 172 583 008 administered COVID-19 vaccines, 43 192 cases met the SAEFVIC inclusion criteria for SIRVA. This equals an incidence of 3.7 cases per 100 000 vaccines administered during the three years. Female subjects are disproportionately affected, with 33 828 cases (77.9 %). The incidence was higher with some COVID-19 vaccine formulations than others. By vaccine type, incidence ranged from 0.4 per 100 000 to 8 per 100 000 and it was lowest (0.4 per 100 000) for NVX-COV2373.

Conclusion

The incidence found in this study is higher than previously reported. The data also reflects that it affects more female subjects than males. While previously considered avoidable using the correct vaccine administration technique, the data challenges this notion as it shows that certain vaccine formulations may be associated with a higher incidence of the condition. The causes of SIRVA are likely multifaceted, with current understanding being further impacted by unclear definitions and reporting requirements.

MAH comment:

This study suggests that vaccine formulation (antigens and adjuvants) may also play a role in the development of SIRVA. However, potential confounding factors such as country of administration, levels of training of immunizers, and patient characteristics may be important considerations, and preclude interpretation of these estimates as direct effects. Case-level data, including for controls, would be required for further evaluation of these effects, perhaps via case-control design. Female subjects have been demonstrated to mount higher immunological responses to vaccination due to sex-linked immune response genes, which may explain the higher rates of SIRVA in female subjects. Overall, knowledge and understanding of SIRVA is largely hampered by a lack of uniform definitions, and poor reporting frameworks. The MAH will continue to monitor the cases of SIRVA through routine PV activities.

Other periodic report

The COVID 19 vaccine is not available as FDC. According to the MAH, during the reporting interval, this is the only PBRER prepared by the MAH for this product.

No other periodic reports prepared by contractual partner for COVID 19 vaccine have been made available to the MAH during the reporting interval.

Rapporteur assessment comment:

During the reporting period one clinical trial was completed (Study 2019nCoV-315 safety and immunogenicity of an Omicron JN.1 subvariant vaccine) and one trial was erroneously considered and reported as ongoing during the previous reporting (Study 2019nCoV-205 High Dose SARS-CoV-2rS

Vaccines Booster).

There were no clinically important emerging efficacy findings and clinically important emerging safety findings in studies completed during the reporting interval.

During the reporting period 4 clinical trials were ongoing (Study 2019nCoV-503, Study 2019nCoV-318 (Sanofi VBV23344), Study 2019nCoV-420, and Study 2019nCoV-415). During the PBRER reporting interval, no interim analyses were planned or conducted for any of the ongoing clinical trials. There was no new clinically important information arising from studies ongoing during the reporting interval.

During the reporting interval, three PASS and three PAES were ongoing. There was also one collaborative research PAES study (BEEHIVE) ongoing during the reporting interval. According to the MAH, there were no safety or efficacy findings relevant to the benefit-risk assessment identified from non-interventional studies during the reporting interval.

52 cases of medication error were reported during the reporting period, the MAH stated that no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMMs) at this time, which is considered acceptable.

Literature research of the MAH retrieved one publication containing new and significant safety findings. The article concluded, that incidence of shoulder injury related to vaccine administration (SIRVA) is higher than previously reported.

MAH stated, that potential confounding factors such as country of administration, levels of training of immunizers, and patient characteristics may be important considerations, and preclude interpretation of these estimates as direct effects. Case-level data, including for controls, would be required for further evaluation of these effects.

MAH noted that cases of SIRVA will be continued monitored through routine PV activities, which is considered acceptable.

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

1.3.6. Lack of efficacy in controlled clinical trials

The MAH states that during the reporting interval no new controlled clinical trials indicating a lack of efficacy of COVID-19 vaccine in the authorized indications, relevant for the benefit-risk evaluation were identified.

1.3.7. Late-breaking information

The MAH did not receive new information regarding potentially important safety or efficacy and/or effectiveness pertaining to COVID 19 vaccine since the DLP for this PBRER.

Rapporteur assessment comment:

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

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 7: Summary of safety concerns at the beginning of the reporting interval (RMP version 6.1, dated 31 October 2024; PSUR p. 171)

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

2.2. Signal evaluation

The MAH notes that there were no signals that were ongoing at the DLP or closed during the reporting interval.

Rapporteur assessment comment:

During the reporting period, no new signals were generated, no signals were ongoing and no signals were closed.

2.3. Evaluation of risks and safety topics under monitoring

TOPICS REQUESTED BY A REGULATORY AUTHORITY TO BE MONITORED IN THE PBRER

Although there was no signal, all cases with a fatal outcome and vaccination failure were reviewed during the period.

Fatal cases

A total of 17 cases with fatal outcome were reported during the review period.

Cases with Nuvaxovid:

Nine cases with fatal outcome were reported during the review period (with age range 26 years to 100 years). These nine cases included 23 fatal AEs coded to PTs: *Hypersensitivity* (n = 4), *Pyrexia* (n = 2), *Headache* (n = 2), *Dyspnoea* (n = 2), *Urticaria* (n = 2), *Rash* (n = 2), *Shock haemorrhagic* (n = 1), *Coronary artery thrombosis* (n = 1), *Sudden death* (n = 1), *Gastric cancer* (n = 1), *Metastasis to liver* (n = 1), *Adverse event* (n = 1), *Cardiovascular disorder* (n = 1), *Acute respiratory failure* (n = 1) and *Death* (n = 1).

In two of these nine cases, the patient's medical history of chronic cardiac failure, aortic aneurysm and renal disorder can be considered as confounding factors for the reported fatal AEs. In one case, the reported event onset latency was more than two years hence, the causal association with vaccination can be excluded. In the remaining six cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid XBB.1.5:

Four cases with fatal outcome were reported during the review period (with age range 55 years to 92 years). These four cases included 11 fatal AEs coded to PTs: *Myocardial infarction* (n = 1), *Syncope* (n = 1), *Respiratory failure* (n = 1), *Cardiac arrest* (n = 1), *Death* (n = 1), *Sudden death* (n = 1), *Dyspnoea* (n = 1), *Blood pressure decreased* (n = 1), *Oxygen saturation decreased* (n = 1), *Asthenia* (n = 1) and *Pyrexia* (n = 1).

In three of these four cases, the patient's medical history of diabetes mellitus (DM), hypertension, atherosclerosis in the lower limbs, myocardial infarction, hypersensitivity, chronic kidney disease stage 4, atrial fibrillation, angina pectoris, kidney cancer, hypercholesterolemia, COPD, recent contact with the persons tested positive for COVID-19 can be considered as confounding factors for the reported fatal AEs. In the remaining one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid JN.1:

Three cases with fatal outcome were reported during the review period (with age range 71 years to 88 years). These three cases included three fatal AEs coded to PTs: *Myocardial infarction* (n = 1), *Cardiovascular disorder* (n = 1) and *Gastrointestinal haemorrhage* (n = 1).

In two of these three cases, the patient's medical history of hypertension, atrial fibrillation, pulmonary hypertension and concomitant medication warfarin can be considered as confounding factors for the reported fatal AEs. In the remaining one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Unknown manufacturer COVID-19 vaccines:

One case was reported in a 67-year-old patient during the review period. In this case, there is a limited information regarding the medical history, medical condition at the time of vaccination, event onset latency, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Overall, no new safety concern was identified following the evaluation of fatal case reports.

Vaccination failure

A total of 10 cases retrieved for evaluation of vaccination failure were analyzed during the reporting period. These cases are described below.

Cases with Nuvaxovid:

Two cases were retrieved during this review period. The reported PTs related to vaccination failure were: Vaccination failure (n = 1), Drug ineffective (n = 1) and COVID-19 (n = 2). Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and disability or permanent damage (n = 1).

In these cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 150 days to 182 days. In one case, the patient had medical history of infection susceptibility increased which can be considered as confounding factor for COVID-19 infection hence, it is not considered as a case of true vaccination failure. In the remaining case, the reported laboratory investigations and clinical examination following COVID-19 infection were normal. The reported case outcomes were: not recovered/not resolved (n = 1) and unknown (n = 1).

Cases with Nuvaxovid XBB.1.5:

Two cases were retrieved during this review period. The reported PTs related to vaccination failure were: Vaccination failure (n = 2) and COVID-19 (n = 2). Both the cases were serious due to medically significant criteria (n = 2) and disability or permanent damage (n = 1).

In these cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 25 days to 326 days. In one case, the patient had medical history of allergic asthma which can be considered as confounding factor for COVID-19 infection hence, it is not considered as a case of true vaccination failure. In the remaining case, the patient had medical history of COVID-19 infection twice before the vaccination with Nuvaxovid XBB.1.5. However, no additional information regarding clinical course and other laboratory investigations was reported hence, further assessment was not possible. The reported case outcomes were: recovered/resolved (n = 1) and recovered/resolved with sequelae (n = 1).

Cases with Nuvaxovid JN.1:

Five cases were retrieved during this review period. The reported PTs related to vaccination failure were: Vaccination failure (n = 3), Breakthrough COVID-19 (n = 2), Drug ineffective (n = 2), COVID-19 (n = 2) and Coronavirus infection (n = 1). All the cases were serious due to medically significant criteria.

In one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course, event onset latency, laboratory investigations hence, the role of the suspect vaccine could not be assessed. In the remaining four cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 34 days to 88 days. In three of these four cases, the patients had medical history of hypogammaglobulinemia, breast carcinoma and cough variant asthma which can be considered as confounding factors for COVID-19 infection hence, they are not considered as cases of true vaccination failure. In the remaining case, the reported laboratory investigations and clinical examination following COVID-19 infection were normal. The reported case outcomes were: recovered/resolved (n = 4) and recovered/resolved with sequelae (n = 1).

Unknown manufacturer COVID-19 vaccines:

One case was reported during the review period. In this case, the PT of Drug ineffective was reported with dupilumab and not with COVID-19 vaccine.

According to the MAH, based on the available information, no significant safety concern is identified. It is to be noted that as with any vaccine, vaccination with COVID-19 vaccine may not protect 100% of susceptible individuals.

New relevant efficacy and/or effectiveness or vaccine failure findings from published clinical studies performed in authorized indications made available during the reporting interval are further discussed in Section 17.2. (NEWLY IDENTIFIED INFORMATION ON EFFICACY AND EFFECTIVENESS) of this PSUR.

Rapporteur assessment comment:

The MAH conducted a review of fatal cases and cases of vaccination failure that occurred during the designated reporting period, which is in general considered acceptable.

However, the MAH is kindly reminded to ask for relevant information to allow proper analysis and causality assessment of these cases.

New information on important potential risks

The MAH stated, that that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized important potential risk.

Source of new information: Cases retrieved during the review period from safety (global PV) database.

Vaccine associated enhanced disease, including VAERD

- **Results:** During the review period, no new cases of VAED, including VAERD were retrieved for COVID-19 vaccine. In addition, no cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.
- **Discussion:** Cumulatively, there are seven case reports (all serious) of Vaccine associated enhanced disease, including VAERD. The reporting rate of VAED, including VAERD remains low and stable over time.
- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of VAED, including VAERD. The MAH will continue to monitor this important potential risk in the future PBRERs.

Atrial Fibrillation and/or Atrial Flutter

- **Background relevant to the evaluation:** Atrial fibrillation and/or atrial flutter have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Results:** During the review period, eight new cases of atrial fibrillation and/or atrial flutter were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Five cases of atrial fibrillation and/or atrial flutter were retrieved during the review period (age range 45 years to 64 years). The reported PTs in these cases were as following: *Atrial fibrillation* (n = 5) and *Atrial flutter* (n = 1). All the cases were serious due to hospitalization (n = 3) and medically significant criteria (n = 5). The reported case outcomes were: not recovered/not resolved (n = 1), recovered/resolved (n = 2), recovering/resolving (n = 1) and unknown (n = 1). In two cases, the

event of atrial fibrillation and/or atrial flutter can be confounded by concomitant medications amlodipine/olmesartan and tamsulosin; and the patient's ongoing medical condition of mitral valve incompetence, respectively. In one case, the event of atrial fibrillation was reported following myocarditis (the case met Level 2 Brighton Collaboration [BC] case definition for myocarditis). In the remaining two cases, the reported event onset latencies were 235 days and; 10 months and 24 days, respectively hence, the causal role of the suspect vaccine can be excluded.

Cases with Nuvaxovid XBB.1.5:

One case of atrial fibrillation and/or atrial flutter was retrieved in 55-year-old patient during the review period. The reported PT was *Atrial fibrillation* (n = 1). The case was serious due to hospitalization and medically significant criteria. The reported case outcome was recovering/resolving. The reported event can be confounded by the co-suspect medication peginterferon alfa-2a.

Cases with Nuvaxovid JN.1:

Two cases of atrial fibrillation and/or atrial flutter were retrieved during the review period (one aged 67 years and one aged 54 years). In both cases, the PT of *Atrial fibrillation* (n = 2) was reported. Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and life threatening (n = 1). The reported case outcome was recovered/resolved in both the cases. In both the cases, limited information was available regarding the clinical course, medical history and medical condition at the time of vaccination hence, the role of the suspect vaccine could not be assessed.

Unknown manufacturer COVID-19 vaccines:

No new cases of atrial fibrillation and/or atrial flutter were retrieved during the review period.

- **Discussion:** Cumulatively, there are 29 case reports (26 serious and three non-serious) retrieved of Atrial Fibrillation and/or Atrial Flutter. The reporting rate of atrial fibrillation and/or atrial flutter remains low and stable over time.

Conclusion: Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of atrial fibrillation and/or atrial flutter. The MAH will continue to monitor this important potential risk in the future PBRERs.

Cerebrovascular Accident

- **Background relevant to the evaluation:** Cerebrovascular accident has been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.

- **Results:** During the review period, 10 new cases of cerebrovascular accident were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Seven cases of cerebrovascular accident were retrieved during the review period (with age range 20 years to 74 years). The reported PTs in these cases were as following: *Brain stem infarction* (n = 1), *Cerebrovascular accident* (n = 4), *Ischemic stroke* (n = 1), *Cerebral infarction* (n = 1) and *Transient ischemic attack* (n = 1). All the cases were serious due to disability/permanent damage (n = 1), hospitalization (n = 7) and medically significant criteria (n = 6). The reported case outcomes were: not recovered/not resolved (n = 3), recovered/resolved with sequelae (n = 2), recovered/resolved (n = 1) and recovering/resolving (n = 1). In one case, the patient had medical history of cerebral small vessel ischemic disease which can be considered as confounding factor for cerebrovascular accident. In the remaining cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid XBB.1.5:

Two cases of cerebrovascular accident were retrieved during the review period (one aged 32 years and one aged 82 years). The reported PTs in these cases were as following: *Ischemic stroke* (n = 1) and *Thalamic infarction* (n = 1). Both the cases were serious due to hospitalization (n = 1) and medically significant criteria (n = 2). In both the cases, the reported case outcome was unknown. In these cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid JN.1:

One case of cerebrovascular accident was retrieved in an 80-year-old patient during the review period. In this case, the PT of *Cerebrovascular accident* (n = 1) was reported. The case was serious due to hospitalization, life threatening, disability/permanent damage and medically significant criteria. The reported case outcome was unknown. In this case, the reported event can be confounded by ongoing medical conditions of arrhythmia, hypertension, hydrocephalus and dementia.

Unknown manufacturer COVID-19 vaccines:

No new cases of cerebrovascular accident were retrieved during the review period.

- **Discussion:** Cumulatively, there are 24 case reports (all serious) of Cerebrovascular Accident were retrieved. The reporting rate of cerebrovascular accident remains low and stable over time.
- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of cerebrovascular accident. The MAH will continue to monitor this important potential risk in the future PBRERs.

Cranial Nerve VIII Disorders (including Vestibular Neuronitis)

- **Background relevant to the evaluation:** Cranial nerve VIII disorders (including vestibular neuronitis) have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Results:** During the review period, no new cases of cranial nerve VIII disorders (including vestibular neuronitis) were retrieved for COVID-19 vaccine. In addition, no new cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.
- **Discussion:** Cumulatively, no cases of cranial nerve VIII disorders (including vestibular neuronitis) were retrieved for COVID-19 vaccine.
- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of cranial nerve VIII disorders (including vestibular neuronitis). The MAH will continue to monitor this important potential risk in the future PBRERs.

Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)

- **Background relevant to the evaluation:** Ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Results:** During the review period, no new cases of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) were retrieved for COVID-19 vaccine. In

addition, no new cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.

- **Discussion:** Cumulatively, there is one serious case report retrieved with the above-mentioned search. The reporting rate of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI). The MAH will continue to monitor this important potential risk in the future PBRERs.

New information on important identified risks

The MAH has determined that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized important identified risk.

Myocarditis and/or pericarditis

- **Background relevant to the evaluation:** Myocarditis and pericarditis have been reported in male and female adults within 14 days of administering COVID-19 vaccine. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

- **Results:** During the review period, 48 new cases of myocarditis and/or pericarditis were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Forty (40) cases were retrieved for evaluation of myocarditis and/or pericarditis which were analyzed during the review period (16 males and 24 females with age range 18 years to 90 years when reported). These 40 cases included 45 AEs reported to PTs: *Atrioventricular block complete* (n = 1), *Bundle branch block left* (n = 1), *Cardiac failure* (n = 2), *Electrocardiogram abnormal* (n = 1), *Electrocardiogram change* (n = 1), *Extrasystoles* (n = 6), *Left ventricular failure* (n = 2), *Myocarditis* (n = 6), *Myopericarditis* (n = 4), *Pericardial effusion* (n = 3), *Pericarditis* (n = 8), *Red blood cell sedimentation rate increased* (n = 2), *Right ventricular failure* (n = 1), *Sudden death* (n = 1), *Supraventricular tachycardia* (n = 1), *Tachyarrhythmia* (n = 2), *Tachycardia paroxysmal* (n = 1) and *Ventricular extrasystoles* (n = 2). Thirty-five (35) cases were serious due to death (n = 1), life-threatening (n = 3), hospitalization (n = 16) and medically significant criteria (n = 33). The reported case outcomes were: fatal (n = 1), not recovered/not resolved (n = 13), recovered/resolved with sequelae (n = 2), recovered/resolved (n = 5), recovering/resolving (n = 8) and unknown (n = 11). Thirty-four (34) out of these 40 cases do not meet Level 1 - 3 BC case definitions for myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis. Five cases met Level - 2, and one case met Level - 1 BC case definitions for myocarditis and/or pericarditis.

Cases with Nuvaxovid XBB.1.5:

Six cases retrieved for evaluation of myocarditis and /or pericarditis which were analyzed during the reporting period (two male and four females with age range 55 years to 91 years when reported). These six cases included six AEs reported to PTs: *Pericarditis* (n = 2), *Myopericarditis* (n = 1), *Extrasystoles* (n = 1), *Sudden death* (n = 1) and *Cardiac arrest* (n = 1). Five cases were serious due to death (n = 2), hospitalization (n = 4) and medically significant criteria (n = 5). The reported case outcomes were: fatal (n = 2), recovering/resolving (n = 2), recovered/resolved (n = 1) and not recovered/not resolved (n = 1). These cases do not meet Level 1 - 3 BC case definitions for

myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis.

Cases with Nuvaxovid JN.1:

Two cases retrieved for evaluation of myocarditis and /or pericarditis which were analyzed during the reporting period (one male aged 67 years and one individual of unknown age and gender). These two cases included two AEs reported to PTs: *Pericardial effusion* (n = 1) and *Cardiac failure* (n = 1). Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and life threatening (n = 1). The reported case outcomes were: recovered/resolved (n = 1) and unknown (n = 1). These cases do not meet Level 1 - 3 BC case definitions for myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis.

Unknown manufacturer COVID-19 vaccines:

No new cases of myocarditis and/or pericarditis were retrieved during the review period.

- **Discussion:** Cumulatively, there are 167 case reports (139 serious and 28 non-serious) retrieved with the above-mentioned search. The reporting rate of myocarditis and/or pericarditis remains low and stable over time. Myocarditis and/or pericarditis have been mentioned under the following sub-sections of CCDS (refer Appendix 1): ‘Special Warnings and Precautions for Use’ and ‘Undesirable Effects’ reported during postmarketing experience.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of myocarditis and/or pericarditis. The MAH will continue to monitor this important identified risk in the future PBRERs.

Anaphylaxis

- **Background relevant to the evaluation:** Anaphylaxis has been considered as an important identified risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025 however, it is a non-important identified risk as per the current EU-RMP version 7.1 dated 25 February 2025.

- **Results:** During the review period, 24 new cases of anaphylaxis were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Twenty (20) cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (three males and 17 females with age range 23 years to 81 years). The reported PTs in these cases were as following: *Circulatory collapse* (n = 5), *Rash* (n = 8), *Angioedema* (n = 1), *Anaphylactic reaction* (n = 4), *Anaphylactic shock* (n = 3), *Hypersensitivity* (n = 5), *Loss of consciousness* (n = 4), *Hypotension* (n = 1), *Erythema* (n = 2), *Pruritus* (n = 5), *Blood pressure decreased* (n = 1), *Swollen tongue* (n = 3), *Eye irritation* (n = 1), *Vomiting* (n = 1), *Ocular hyperaemia* (n = 1), *Eye swelling* (n = 1), *Cyanosis* (n = 1), *Lip oedema* (n = 1), *Cough* (n = 1), *Rhinorrhoea* (n = 1) and *Urticaria* (n = 2). One case was non-serious while 19 cases were serious due to death (n = 2), life threatening (n = 2), disability/permanent damage (n = 1), hospitalization (n = 5) and medically significant criteria (n = 17). The reported case outcomes were: fatal (n = 2), not recovered/not resolved (n = 5), recovered/resolved with sequelae (n = 1), recovered/resolved (n = 9), recovering/resolving (n = 1) and unknown (n = 2). In two fatal cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. These cases met Level - 4 of the BC case definition for anaphylaxis.

In six of the remaining 18 cases, the patients had medical history of hypersensitivity, allergic rhinitis and urticaria which can be considered as confounding factors for the reported events. In the remaining 12 cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. Overall, two cases met Level - 2, and six cases met Level - 4 of the BC case definition for anaphylaxis. The remaining cases were not considered as cases of anaphylaxis.

Cases with Nuvaxovid XBB.1.5:

Two cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (one male aged 92 years and one female aged 86 years). The reported PTs in these cases were as following: *Oxygen saturation decreased* (n = 2) and *Blood pressure decreased* (n = 1). Both the cases were serious due to death (n = 2), hospitalization (n = 1) and medically significant criteria (n = 1). In both the cases, the reported case outcome was fatal. In these cases, the patients have medical history of hypertension, myocardial infarction, drug hypersensitivity, diabetes mellitus, arteriosclerosis, chronic obstructive pulmonary disease, hypercholesteremia and dementia which can be considered as confounding factors for the reported events and fatal outcome. These cases do not meet the BC case definition for anaphylaxis hence, they are not considered as cases of anaphylaxis.

Cases with Nuvaxovid JN.1:

Two cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (one female aged 38 years and one elderly female of unknown age). The reported PTs in these cases were as following: *Oxygen saturation decreased* (n = 2), *Pruritus* (n = 1), *Urticaria* (n = 1), *Stridor* (n = 1), *Cough* (n = 1), *Swelling face* (n = 1), *Rash pruritic* (n = 1), *Rhinorrhoea* (n = 1) and *Swelling of eyelid* (n = 1). Both the cases were serious due to hospitalization (n = 1) and medically significant criteria (n = 2). The reported case outcomes were: not recovered/not resolved (n = 1) and recovered/resolved (n = 1). In these cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. These cases do not meet the BC case definition for anaphylaxis hence, they are not considered as cases of anaphylaxis.

Unknown manufacturer COVID-19 vaccines:

No new cases of anaphylaxis were reported during the review period.

• **Discussion:** Cumulatively, there are 176 case reports (106 serious and 70 non-serious) retrieved with the above-mentioned search. The reporting rate of anaphylaxis remains low and stable over time.

Conclusion: Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of anaphylaxis. The MAH will continue to monitor this important identified risk in the future PBRERs.

New information on other identified risks not categorized as important

The MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of previously recognized identified risk not categorized as important or warrants further discussion in the PBRER.

Update on missing information

According to the MAH, no new safety information has been identified during the reporting interval that would have an impact on the understanding and characterization of missing information or warrants further discussion in the PBRER.

Rapporteur assessment comment:

The MAH reviewed cases retrieved during the reporting period from safety (global PV) database for the important potential risks and important identified risks for COVID-19 vaccine.

The MAH stated, that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized important potential risk and important identified risk.

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

2.4. Characterisation of risks

A characterisation of the important identified and important potential risks as well as missing information was provided.

Rapporteur assessment comment:

The safety concerns remain unchanged.

3. Benefit evaluation

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

Baseline effectiveness of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 for individuals 12 years of age and older was inferred from studies which evaluated the primary series and booster vaccination with COVID-19 vaccine Original, Wuhan strain and was supported by a study of a booster dose of an investigational vaccine targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 and BA.5 variants of SARS-CoV-2 in individuals 18 to 64 years of age.

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

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

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

According to the MAH, the efficacy of Novavax COVID-19 Vaccine (recombinant, adjuvanted) was consistent between elderly (≥ 65 years) and younger individuals (18 to 64 years) for the primary series. Participants ≥ 65 years of age were evaluated for efficacy in the two pivotal Phase 3 clinical trials. In the placebo-controlled Phase 3 Study 2019nCoV-301 conducted in the US and Mexico, 11.8% ($n = 2048$) of enrolled participants that received the primary series were ≥ 65 years. In the placebo-controlled Phase 3 Study 2019nCoV-302 conducted in the UK, 27.8% ($n = 1953$) of enrolled participants who received the primary series were ≥ 65 years.

The MAH presents a subsection providing information that became available in the literature (7 publications) during the reporting interval of this PBRER, on the efficacy/effectiveness or/and safety and immunogenicity of Nuvaxovid vaccines.

The MAH stated, that no new relevant efficacy and/or effectiveness findings in approved indications were identified during the reporting interval.

Rapporteur assessment comment:

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

4. Benefit-risk balance

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

5. Rapporteur Request for supplementary information

With regard to 'New Safety Data Related to Fixed Combination Therapies', the MAH stated within the last reporting period, that there was one NVX-sponsored Phase 3 clinical trial (2019nCoV-CIC-E-301, investigating the CIC vaccine comprising the JN.1-variant adapted COVID-19 vaccine (NVX-CoV-2705) co-formulated with the trivalent nanoparticle influenza hemagglutinin vaccine (tNIV) with Matrix-M™ adjuvant) ongoing. However, within this PSUR the MAH stated, that the section '7.5 New Safety Data Related to Fixed Combination Therapies' is not applicable since the development program does not include a fixed combination product or a multi-drug regimen.

The MAH is kindly requested to shortly comment on the status of this study and whether there are any safety finding arise from this study during the reporting period.

With regard to '9.1 OTHER CLINICAL TRIALS', the MAH stated within the last reporting period, that, there were three ongoing investigator-initiated studies. However, within this reporting period the MAH stated, this section is not applicable as no other clinical trial/study were ongoing or completed during the reporting period.

The MAH is kindly asked to shortly comment on the status of these studies and comment on whether there are any safety findings from these studies.

The MAH stated within the last PSUR, that there was one collaborative surveillance study (2019nCoV-413) ongoing during the reporting period, this study is not mentioned in the current PSUR. Therefore, the MAH is kindly asked to shortly comment on the status of this study and whether there is any safety findings arise from this study.

6. MAH responses to Request for supplementary information

Question 1:

With regard to 'New Safety Data Related to Fixed Combination Therapies', the MAH stated within the last reporting period, that there was one NVX-sponsored Phase 3 clinical trial (2019nCoV-CIC-E-301, investigating the CIC vaccine comprising the JN.1-variant adapted COVID-19 vaccine (NVX-CoV-2705) co-formulated with the trivalent nanoparticle influenza hemagglutinin vaccine (tNIV) with Matrix-M™ adjuvant) ongoing. However, within this PSUR the MAH stated, that the section '7.5 New Safety Data Related to Fixed Combination Therapies' is not applicable since the development program does not include a fixed combination product or a multi-drug regimen.

The MAH is kindly requested to shortly comment on the status of this study and whether there are any safety findings arise from this study during the reporting period.

MAH response:

The MAH confirms that Novavax sponsored study **2019nCoV-CIC-E-301** - A Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety and Immunogenicity of a COVID-19 Influenza Combination Nanoparticle Vaccine and a Standalone Trivalent Nanoparticle Influenza Hemagglutinin Vaccine in Participants ≥ 65 Years of Age is still ongoing.

There were no safety signals identified during the reporting period.

Question 2:

With regard to '9.1 OTHER CLINICAL TRIALS', the MAH stated within the last reporting period, that, there were three ongoing investigator-initiated studies. However, within this reporting period the MAH stated, this section is not applicable as no other clinical trial/study were ongoing or completed during the reporting period. The MAH is kindly asked to shortly comment on the status of these studies and comment on whether there are any safety findings from these studies.

MAH response:

The MAH is providing below information on the status of these studies and hereby confirms that:

- **Study CoM-COV-3** - A single-blind randomised, Phase II multicentre study to determine Reactogenicity And Immunogenicity of heterologous prime/boost COVID-19 Vaccine schedules in adolescents (EudraCT 2021-004267-27) has been completed as of 30 September 2024, and no new safety findings have been identified (1) (2).
- **IND 027485 NIAID Beigel** - Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines (NCT04889209 / 21-0012) has been completed as of 16 June 2023, and no new safety findings have been identified (3).
- **Vienna Zeitlinger study** - Safety and immunogenicity of concomitant administration of the Novavax vaccine and a 20-valent pneumococcal conjugate vaccine in adults aged ≥60 years: a four-arm, double-blind, non-inferiority trial (EudraCT 2022-004118-12) has been completed as of 03 June 2024, and no new safety findings have been identified (4).

Question 3:

The MAH stated within the last PSUR, that there was one collaborative surveillance study (2019nCoV-413) ongoing during the reporting period, this study is not mentioned in the current PSUR. Therefore, the MAH is kindly asked to shortly comment on the status of this study and whether there is any safety findings arise from this study.

MAH response:

The MAH confirms that collaborative surveillance study **2019nCoV-413** has been completed as of 02 October 2025 and that no new safety findings have been identified.

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3. Lyke KE, Atmar RL, Dominguez Islas C, et al. Immunogenicity of NVX-CoV2373 heterologous boost against SARS-CoV-2 variants. *npj Vaccines*, 8:98, (2023). <https://doi.org/10.1038/s41541-023-00693-z>
4. Jorda A, Prager M, Pracher L, et al. Immunogenicity, Safety, and Reactogenicity of Concomitant Administration of the Novavax Vaccine Against Omicron XBB.1.5 (NVXCoV2601) and a 20-Valent Pneumococcal Conjugate Vaccine in Adults Aged ≥ 60 Years: A Randomised, Double-Blind, Placebo-Controlled, Non-Inferiority Trial. *Journal of Infection*, (2025). <https://doi.org/10.1016/j.jinf.2024.106405>

Rapporteur assessment comment:

The MAH provided an update on the status of the requested clinical trials and confirmed that no safety concerns had arisen during the reporting period. The issue is considered resolved.

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PERIODIC BENEFIT RISK EVALUATION REPORT

COVID-19 Vaccine (recombinant, adjuvanted)

Covered period: 20-Dec-2024 to 19-Dec-2025

International Birth Date (IBD): 20-Dec-2021

Report reference: VV-PV-0624199
Name: [REDACTED] MD, MPH
Function: Global Safety Officer
By delegation from the Sanofi QPPV
Signature: Signature on file

Date: 19-Feb-2026

Total number of pages: 83 (+Appendices)

EXECUTIVE SUMMARY

This Periodic Benefit Risk Evaluation Report (PBRER) for Coronavirus Disease 2019 (COVID-19) vaccine (recombinant, adjuvanted), was prepared in accordance with the content and format proposed by the International Conference on Harmonization (ICH) guideline (ICH E2C [R2] step 5): PBRER and Guideline on Good Pharmacovigilance Practices Module VII – Periodic Safety Update Report (revision #1).

It summarizes the cumulative safety information for the Marketing Authorization Holder's (MAH's) products containing COVID-19 vaccine, received by Sanofi's Patient Safety & Pharmacovigilance (PSPV) department from worldwide sources, from 20 December 2024 through 19 December 2025.

The term "original vaccine" refers to Nuvaxovid®, the term "XBB.1.5 vaccine" refers to Nuvaxovid XBB.1.5, the term "JN.1 vaccine" refers to Nuvaxovid JN.1 and the term "COVID-19 vaccine" refers to Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1, hereafter referred to as "COVID-19 vaccine".

The COVID-19 vaccine belongs to the therapeutic class of COVID-19, protein subunit.

The COVID-19 vaccine is composed of purified full-length severe acute respiratory syndrome coronavirus 2 recombinant spike protein (SARS-CoV-2rS) that is stabilized 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 spike protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the spike protein, including neutralizing antibodies, which may protect against COVID-19.

The COVID-19 vaccine is approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

The COVID-19 vaccine is available as colorless to slightly yellow and clear to mildly opalescent dispersion for injection. It is available as one single-dose vial which contains one dose of 0.5 mL, one multidose vial which contains five or 10 doses of 0.5 mL per vial, and one single-dose pre-filled syringe which contains one dose of 0.5 mL; administered as an intramuscular injection only. One dose (0.5 mL) contains: 5 micrograms of the SARS-CoV-2rS and is adjuvanted with Matrix-M.

A Pharmacovigilance (PV) divestment agreement is in place between Sanofi-Aventis Research & Development (R&D) and NOVAVAX INC. This PBRER includes all the individual case safety reports (ICSRs) received by this Purchaser and transmitted to Sanofi PSPV.

Nuvaxovid:

The first marketing authorization (MA) for Nuvaxovid was obtained in the European Union (EU) on 20 December 2021.

Nuvaxovid is approved in 48 countries worldwide (including Sanofi and Partner territories).

During the period covered by this report, a MA for Nuvaxovid was granted in the United States (US) on 16 May 2025 and in Israel on 10 August 2025.

Nuvaxovid is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, as a two-dose primary series and as a booster for individuals 12 years and older in multiple countries at the following doses:

- Primary vaccination series: Administered intramuscularly as a course of two doses of 0.5 mL each. It is recommended to administer the second dose three weeks after the first dose.
- Booster dose: Administered intramuscularly approximately three months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose). Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of a messenger ribonucleic acid vaccine or adenoviral vector vaccine (heterologous booster dose).

In countries where Serum Institute of India Pvt Ltd. (SIPL) is the MAH, the alternative name for Nuvaxovid is Covovax®. In India, Covovax is authorized as a two-dose primary series in individuals seven years of age and older and as a booster for individuals 18 years of age and older. In Japan, where Takeda is the MAH, Nuvaxovid is authorized as a two-dose primary series in individuals six years of age and older and as booster in individuals 12 years of age and older.

Nuvaxovid is prequalified by the World Health Organization (WHO) since 20 December 2021 as part of Emergency Use Listing (EUL).

Nuvaxovid XBB.1.5:

The first MA for Nuvaxovid XBB.1.5 was obtained in the US on 03 October 2023.

Nuvaxovid XBB.1.5 is approved in 38 countries worldwide (including Sanofi and Partner territories). During the period covered by the report, Nuvaxovid XBB.1.5 did not receive additional MA.

Nuvaxovid XBB.1.5 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.
For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least three months after the most recent dose of a COVID-19 vaccine.
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In Brazil and India, where SIIPL is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula). In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Novavax COVID-19 Vaccine, Adjuvanted 2023-2024 formula.

Nuvaxovid XBB.1.5 is prequalified by the WHO since 22 November 2023 as part of the EUL.

Nuvaxovid JN.1:

The first MA for Nuvaxovid JN.1 was obtained in the US on 30 August 2024.

Nuvaxovid JN.1 is approved in 37 countries worldwide (including Sanofi and Partner territories).

During the period covered by the report, a MA for Nuvaxovid JN.1 was granted in three countries, including the US on 16 May 2025 (2024-2025 Formula) and 27 August 2025 (2025-2026 Formula), Taiwan on 26 May 2025 and in the United Kingdom (UK) on 29 August 2025.

During the period covered by the report, the Emergency Use Authorization (EUA) was withdrawn in the US on 27 August 2025 (EUA 28237), following the above-mentioned BLA approval.

Nuvaxovid JN.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.
For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least three months after the most recent dose of a COVID-19 vaccine.
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations

In the US, Nuvaxovid JN.1 (Nuvaxovid COVID-19 Vaccine, Adjuvanted [2025-2026 Formula]) is approved for use in individuals who are:

- 65 years of age and older, or
- 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid JN.1 is Novavax COVID-19 Vaccine 2024-2025 formula.

Nuvaxovid JN.1 is prequalified by the WHO since 26 June 2025.

Nuvaxovid LP.8.1:

The first MA for Nuvaxovid LP.8.1 was obtained in Japan and is part of a licensing agreement between Novavax and Takeda.

Nuvaxovid LP.8.1 is only approved in one country (Japan) worldwide.

During the period covered by the report, a MA for Nuvaxovid LP.8.1 was granted in Japan on 27 August 2025.

Nuvaxovid LP.8.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 as an initial immunization (first and second vaccination) for those aged six years or older and a booster immunization (after the third vaccination) for those aged 12 years or older.

Cumulatively, there were approximately 58 665 participants exposed to COVID-19 vaccine in MAH-sponsored clinical trials.

For Sanofi, there was no sales data retrieved for the cumulative period (20 December 2021 to 19 December 2025) as well as for the interval period (20 December 2024 to 19 December 2025).

For Partner Novavax, sales figures for the interval period were received for the period from 20 December 2024 to 19 December 2025. Exposure from the cumulative experience is available from 20 December 2021 to 19 December 2025¹. The total doses distributed during the interval period for Nuvaxovid JN.1 is 2 567 000. No doses were distributed for Nuvaxovid and Nuvaxovid XBB.1.5 during the interval period. The total doses distributed during the cumulative period for Nuvaxovid is 104 284 800, for Nuvaxovid XBB.1.5 is 18 134 270, and for Nuvaxovid JN.1 is 5 914 840.

Based on the sales figure available from Sanofi and partner Novavax, the overall COVID-19 vaccine doses distributed during the cumulative period is estimated to be 128 333 910 and the overall COVID-19 vaccine doses distributed during the interval period is estimated to be 2 567 000.

No actions were taken for safety reasons during the period covered by this report.

The company core data sheet (CCDS) for COVID-19 vaccine, version 10 dated 30 May 2024 was the reference safety information (RSI) valid at the beginning of the PBRER period.

¹ The distribution data provided includes all distribution since the International Birth Date (20-Dec-2021) till 19-Dec-2025. The first Novavax commercial shipment was in February 2022, and there have been no additional shipments since November 2025.

The RSI was revised to:

- The CCDS version 11, dated 04 February 2025, and the following amendments were made:
 - Adverse reactions section
 - o Updated the incidence percentages of most frequently reported adverse reactions in adults following a booster dose, based on data from final clinical study report from studies 2019nCoV-101 Part 2, 2019nCoV-301 and 2019nCoV-311 Part 1
 - o Editorial updates throughout the section.
- The CCDS version 12, dated 11 June 2025, and the following amendments were made:
 - Adverse reactions section was revised to:
 - o Update the incidence percentages of most frequently reported adverse reactions based on data from studies 2019nCoV-301 (adolescents and adults populations) and 2019nCoV-311 Part 2 (adults populations).
 - Clinical Efficacy section was updated to:
 - o Revise final efficacy and immunogenicity, based on final data from Study 2019nCoV-301 in adolescents aged 12 to 17 years.
 - o Revise immunogenicity data following booster dose administration in adults, as per final data from Study 2019nCoV-301
 - o Revise the number of participants from Study 2019nCoV-311, Part 2

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older remains positive in the currently approved conditions of use.

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ABBREVIATIONS

adjOR:	Adjusted Odds Ratio
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Events of Special Interest
aHR:	Adjusted Hazard Ratio
BC:	Brighton Collaboration
CCDS:	Company Core Data Sheet
CI:	Confidence Interval
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19:	Coronavirus Disease 2019
CSR:	Clinical Study Report
DIBD:	Development International Birth Date
DLP:	Data Lock Point
DM:	Diabetes Mellitus
ED:	Extension Day
ELISA:	Enzyme-Linked Immunosorbant Assay
EU:	European Union
EUA:	Emergency Use Authorization
EUL:	Emergency Use Listing
FDC:	Fixed Dose Combination
GMEU:	Geometric Mean ELISA unit
GMR:	Geometric Mean Ratio
GMT:	Geometric Mean Titre
GVP:	Good Pharmacovigilance Practices
HIV:	Human Immunodeficiency Virus
HLT:	High Level Term
IBD:	International Birth Date
ICH:	International Conference on Harmonization
ICSR:	Individual Case Safety Report
ID ₅₀ :	Inhibitory Dilution at a Concentration of 50%
IgG:	Immunoglobulin G
IND:	Investigational New Drug
MA:	Marketing Authorization
MAH:	Marketing Authorization Holder
MC:	Molecular Clamp
MedDRA:	Medical Dictionary for Regulatory Activities
MN ₅₀ :	Microneutralization Assay of the Dilution to Achieve 50% Neutralization
mRNA:	Messenger Ribonucleic Acid
nAbs:	Neutralizing Antibody

PAES:	Post-Authorization Efficacy Studies
PASS:	Post-Authorization Safety Studies
PBRER:	Periodic Benefit Risk Evaluation Report
PCR:	Polymerase Chain Reaction
PLHIV:	People living with human immunodeficiency virus
PP-EFF:	Per Protocol-Efficacy
PP-IMM:	Per Protocol Immunogenicity
PSPV:	Patient Safety and Pharmacovigilance
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
PV:	Pharmacovigilance
PWH:	People with human immunodeficiency virus
PWoH:	People without human immunodeficiency virus
PY:	Person years
R&D:	Research and Development
RBD:	Receptor Binding Domain
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
RSI:	Reference Safety Information
SAE:	Serious Adverse Event
SAEFVIC:	Surveillance of Adverse Events Following Vaccination In the Community
SARS:	Severe Acute Respiratory Syndrome
SARS-CoV:	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2rS:	Severe acute respiratory syndrome coronavirus 2 recombinant spike protein
SCR:	Seroconversion Rate
SIPL:	Serum Institute of India Pvt Ltd.
SIRVA:	Shoulder injury related to vaccine administration
SmPC:	Summary of product Characteristics
SMQ:	Standardized MedDRA Query
SRR:	Sero Response Rate
TEAE:	Treatment emergent adverse event
UK:	United Kingdom
US:	United States
VAED:	Vaccine Associated Enhanced Disease
VAERD:	Vaccine Associated Enhanced Respiratory Disease
VOC:	Variant of Concern
VOI:	Variants of Interest
WHO:	World Health Organization

1 INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) for Coronavirus Disease 2019 (COVID-19) vaccine (recombinant, adjuvanted), was prepared in accordance with the content and format proposed by the International Conference on Harmonization (ICH) guideline (ICH E2C [R2] step 5): PBRER and Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report (PSUR) (revision #1).

It summarizes the cumulative safety information for the Marketing Authorization Holder (MAH) products containing COVID-19 vaccine, received by the MAH's Patient Safety & Pharmacovigilance (PSPV) department from worldwide sources, from 20 December 2024 through 19 December 2025.

The term "original vaccine" refers to Nuvaxovid®, the term "XBB.1.5 vaccine" refers to Nuvaxovid XBB.1.5, the term "JN.1 vaccine" refers to Nuvaxovid JN.1 and the term "COVID-19 vaccine" refers to Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1, hereafter referred to as "COVID-19 vaccine".

The International Birth Date (IBD) of COVID-19 vaccine is 20 December 2021.

The COVID-19 vaccine belongs to the therapeutic class of COVID-19, protein subunit.

The COVID-19 vaccine is composed of purified full-length severe acute respiratory syndrome coronavirus 2 recombinant spike protein (SARS-CoV-2rS) that is stabilized 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 spike protein-specific immune response. The two vaccine components elicit B- and T-cell immune responses to the spike protein, including neutralizing antibodies (nAbs), which may protect against COVID-19.

The COVID-19 vaccine is approved for active immunization to prevent COVID-19 caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older.

The COVID-19 vaccine is available as colorless to slightly yellow and clear to mildly opalescent dispersion for injection. It is available as one single-dose vial which contains one dose of 0.5 mL, one multidose vial which contains five or 10 doses of 0.5 mL per vial, and one single-dose pre-filled syringe which contains one dose of 0.5 mL; administered as an intramuscular injection only. One dose (0.5 mL) contains: 5 micrograms of the SARS-CoV-2rS and is adjuvanted with Matrix-M.

Nuvaxovid:

Nuvaxovid is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, as a two-dose primary series and as a booster for individuals 12 years and older in multiple countries at the following doses:

- Primary vaccination series: Administered intramuscularly as a course of two doses of 0.5 mL each. It is recommended to administer the second dose three weeks after the first dose.
- Booster dose: Administered intramuscularly approximately three months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose). Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of a messenger ribonucleic acid (mRNA) vaccine or adenoviral vector vaccine (heterologous booster dose).

In countries where Serum Institute of India Pvt Ltd. (SIPL) is the MAH, the alternative name for Nuvaxovid is Covovax®. In India, Covovax is authorized as a two-dose primary series in individuals seven years of age and older and as a booster for individuals 18 years of age and older. In Japan, where Takeda is the MAH, Nuvaxovid is authorized as a two-dose primary series in individuals six years of age and older and as booster in individuals 12 years of age and older.

Nuvaxovid XBB.1.5:

Nuvaxovid XBB.1.5 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.
For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least three months after the most recent dose of a COVID-19 vaccine.
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In Brazil and India, where SIPL is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula). In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Novavax COVID-19 Vaccine, Adjuvanted 2023-2024 formula.

Nuvaxovid JN.1:

Nuvaxovid JN.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.
For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least three months after the most recent dose of a COVID-19 vaccine.
- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In the US, Nuvaxovid JN.1 (Nuvaxovid COVID-19 Vaccine, Adjuvanted [2025-2026 Formula]) is approved for use in individuals who are:

- 65 years of age and older, or
- 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid JN.1 is Novavax COVID-19 Vaccine 2024-2025 formula.

Nuvaxovid LP.8.1:

Nuvaxovid LP.8.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 as an initial immunization (first and second vaccination) for those aged six years or older and a booster immunization (after the third vaccination) for those aged 12 years or older.

A Pharmacovigilance (PV) divestment agreement is in place between Sanofi-Aventis Research & Development (R&D) and NOVAVAX INC. This PBRER includes all the individual case safety reports (ICSRs) received by this Purchaser and transmitted to Sanofi PSPV.

The COVID-19 vaccine is not available as fixed dose combination (FDC). During the reporting interval, this is the only PBRER prepared by the MAH for this product.

No other periodic reports prepared by contractual partner for COVID-19 vaccine have been made available to the MAH during the reporting interval.

2 WORLDWIDE MARKETING APPROVAL STATUS

Nuvaxovid:

The first marketing authorization (MA) for Nuvaxovid was obtained in the European Union (EU) on 20 December 2021. The detailed cumulative worldwide marketing approval status is provided in [Appendix 5.1.1](#) and [Appendix 5.1.2](#).

Nuvaxovid is approved in 48 countries worldwide (including Sanofi and Partner territories).

During the period covered by this report, a MA for Nuvaxovid was granted in the United States (US) on 16 May 2025 and in Israel on 10 August 2025.

Nuvaxovid is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, as a two-dose primary series and as a booster for individuals 12 years and older in multiple countries at the following doses:

- Primary vaccination series: Administered intramuscularly as a course of two doses of 0.5 mL each. It is recommended to administer the second dose three weeks after the first dose.
- Booster dose: Administered intramuscularly approximately three months after the primary series of Nuvaxovid in individuals 12 years of age and older (homologous booster dose). Nuvaxovid may also be given as a booster dose in individuals 18 years of age and older following a primary series comprised of an mRNA vaccine or adenoviral vector vaccine (heterologous booster dose).

In countries where SIIPL is the MAH, the alternative name for Nuvaxovid is Covovax. In India, Covovax is authorized as a two-dose primary series in individuals seven years of age and older and as a booster for individuals 18 years of age and older. In Japan, where Takeda is the MAH, Nuvaxovid is authorized as a two-dose primary series in individuals six years of age and older and as booster in individuals 12 years of age and older.

Nuvaxovid is prequalified by the World Health Organization (WHO) since 20 December 2021 as part of the Emergency use listing (EUL).

Nuvaxovid XBB.1.5:

The first MA for Nuvaxovid XBB.1.5 was obtained in the US on 03 October 2023. The detailed cumulative worldwide marketing approval status is provided in [Appendix 5.1.1](#) and [Appendix 5.1.2](#).

Nuvaxovid XBB.1.5 is approved in 38 countries worldwide (including Sanofi and Partner territories).

During the period covered by the report, Nuvaxovid XBB.1.5 did not receive additional MA.

Nuvaxovid XBB.1.5 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid XBB.1.5 should be administered at least three months after the most recent dose of a COVID-19 vaccine.

- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In Brazil and India, where SIIPL is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Covovax COVID-19 Vaccine Adjuvanted (2023-2024 Formula). In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid XBB.1.5 is Novavax COVID-19 Vaccine, Adjuvanted 2023-2024 formula.

Nuvaxovid XBB.1.5 is prequalified by the WHO since 22 November 2023 as part of the EUL.

Nuvaxovid JN.1:

The first MA for Nuvaxovid JN.1 was obtained in the US on 30 August 2024. The detailed cumulative worldwide marketing approval status is provided in [Appendix 5.1.1](#) and [Appendix 5.1.2](#).

Nuvaxovid JN.1 is approved in 37 countries worldwide (including Sanofi and Partner territories).

During the period covered by the report, a MA for Nuvaxovid JN.1 was granted in three countries, including the US on 16 May 2025 (2024-2025 Formula) and 27 August 2025 (2025-2026 Formula), Taiwan on 26 May 2025 and in the United Kingdom (UK) on 29 August 2025.

During the period covered by the report, the Emergency Use Authorization (EUA) was withdrawn in the US on 27 August 2025 (EUA 28237), following the above-mentioned BLA approval.

Nuvaxovid JN.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older at the following doses:

- Administered intramuscularly as a single dose (0.5 mL) for individuals 12 years of age and older regardless of previous vaccination status.

For individuals who have previously been vaccinated with a COVID-19 vaccine, Nuvaxovid JN.1 should be administered at least three months after the most recent dose of a COVID-19 vaccine.

- Additional doses may be administered to individuals who are severely immunocompromised in accordance with national recommendations.

In the US, Nuvaxovid JN.1 (Nuvaxovid COVID-19 Vaccine, Adjuvanted [2025-2026 Formula]) is approved for use in individuals who are:

- 65 years of age and older, or
- 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In South Korea, where SK Bioscience Co., Ltd is the MAH, the alternative name for Nuvaxovid JN.1 is Novavax COVID-19 Vaccine 2024-2025 formula.

Nuvaxovid JN.1 is prequalified by the WHO since 26 June 2025.

Nuvaxovid LP.8.1:

The first MA for Nuvaxovid LP.8.1 was obtained in Japan and is part of a licensing agreement between Novavax and Takeda. The detailed cumulative worldwide marketing approval status is provided in [Appendix 5.1.2](#).

Nuvaxovid LP.8.1 is only approved in one country (Japan) worldwide.

During the period covered by the report, a MA for Nuvaxovid LP.8.1 was granted in Japan on 27 August 2025.

Nuvaxovid LP.8.1 is approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 as an initial immunization (first and second vaccination) for those aged six years or older and a booster immunization (after the third vaccination) for those aged 12 years or older.

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

No actions were taken during the reporting interval for safety reasons related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), Regulatory Authorities, data monitoring committees, or ethics committees that had:

- A significant influence on the risk-benefit profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The company core data sheet (CCDS) for COVID-19 vaccine, version 10 dated 30 May 2024 was the reference safety information (RSI) valid at the beginning of the PBRER period.

The RSI was revised to:

- The CCDS version 11, dated 04 February 2025, and the following amendments were made:
 - Adverse reactions section
 - o Updated the incidence percentages of most frequently reported adverse reactions in adults following a booster dose, based on data from final clinical study report (CSR) from studies 2019nCoV-101 Part 2, 2019nCoV-301 and 2019nCoV-311 Part 1.
 - o Editorial updates throughout the section.
- The CCDS version 12, dated 11 June 2025, and the following amendments were made:
 - Adverse reactions section was revised to:
 - o Update the incidence percentages of most frequently reported adverse reactions based on data from studies 2019nCoV-301 (adolescents and adults populations) and 2019nCoV-311 Part 2 (adults populations).
 - Clinical Efficacy section was updated to:
 - o Revise final efficacy and immunogenicity, based on final data from Study 2019nCoV-301 in adolescents aged 12 to 17 years.
 - o Revise immunogenicity data following booster dose administration in adults, as per final data from Study 2019nCoV-301.
 - o Revise the number of participants from Study 2019nCoV-311, Part 2.

The current RSI at the data lock point (DLP) is the CCDS version 12, dated 11 June 2025 attached in [Appendix 1](#).

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 CUMULATIVE SUBJECT EXPOSURE IN CLINICAL TRIALS

This section presents estimates of cumulative numbers of participants, from ongoing or completed MAH-sponsored clinical trials, exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the development international birth date (DIBD).

The cumulative exposure to COVID-19 vaccine in interventional clinical trials sponsored by the MAH is estimated to be 58 665 participants. Exposure data from clinical trials is presented [Table 1](#).

Table 1 - Cumulative Participant Exposure by Clinical Trial and Study Treatment

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototy pe	Prototy pe+BA. 1	Prototy pe+BA. 5	XBB.1 .5	Prototy pe+XB B.1.5	JN.1	Blinded Treatme nt	Total (Excl. Place bo)
2019nCoV-101 Part 1	23	–	–	–	108	–	–	–	–	–	–	108
2019nCoV-101 Part 2	254	–	–	–	1029	–	–	–	–	–	–	1029
2019nCoV-205	–	–	–	–	91	–	–	811	–	–	–	902 ^b
2019nCoV-301 Adult	3458	–	–	–	26 124	–	–	–	–	–	–	26 124
2019nCoV-301 Peds	75	–	–	–	2157	–	–	–	–	–	–	2157
2019nCoV-302	4346	–	–	–	10 792	–	–	–	–	–	–	10 792
2019nCoV-307	–	–	–	–	905	–	–	–	–	–	–	905
2019nCoV-311 Part 1	–	347	–	–	335	269	–	–	–	–	–	951
2019nCoV-311 Part 2	–	–	254	–	251	–	259	–	–	–	–	764
2019nCoV-312	–	–	43	–	104	–	–	–	–	–	–	147

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-313 Part 1	—	—	—	—	—	—	—	332	—	—	—	332
2019nCoV-313 Part 2	—	—	—	—	—	—	—	338	—	—	—	338
2019nCoV-314	—	—	—	—	—	—	—	190	210	—	—	400
2019nCoV-315	—	—	—	—	—	—	—	—	—	60	—	60
2019nCoV-318	—	—	—	—	—	—	—	—	—	676	—	676
2019nCoV-501	304	—	—	—	4104	—	—	—	—	—	—	4104
2019nCoV-415	—	—	—	—	—	—	—	—	—	219	—	219
2019nCoV-420	—	—	—	—	—	—	—	—	—	—	834	834
2019nCoV-503	—	—	—	—	—	—	—	—	—	—	3640	3640 ^c
2019nCoV-505	—	—	—	—	383	—	—	—	—	—	—	383
2019nCoV-ICC-E-101 ^a	—	—	—	558	78	—	—	—	—	—	—	636

Clinical Trial	Number of Participants by Study Treatment											
	Placebo	BA .1	BA .5	CIC ^a	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded Treatment	Total (Excl. Placebo)
2019nCoV-CIC-E-201 ^a	–	–	–	864	315	–	–	–	–	–	–	1179
CIC-E-301 ^a	–	–	–	–	–	–	–	–	–	–	1985	1985
Total	8460	347	297	1422	46776	269	259	1671	210	955	6459	58 665^d

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

^b Ninety-one (91) participants who took mRNA were excluded from the 2019nCoV-205 study total.

^c For Study 503, some participants were identified for cross-enrolment in different sites. For example, the same participant could have three different subject IDs when the participant enrolled in the study from three different sites. In the current statistical programming, unique participants were counted instead of counting all subject IDs. Therefore, the number of participants in Study 503 in the current tables is less than the PBRER No.05 (20-Dec-2023 to 19-Jun-2024) table which counted all subject IDs.

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

CIC: COVID-19 Influenza Combination Nanoparticle Vaccine; mRNA: messenger Ribonucleic acid; PBRER: Periodic Benefit Risk Evaluation Report.

Additional exposure information by age range, gender, and racial group from ongoing and completed clinical trials is provided in [Table 2](#), [Table 3](#), and [Table 4](#).

Table 2 - Cumulative Participant Exposure Stratified by Age

Age	Treatment/Number of Participants											
	Placebo	BA.1	BA.5	CIC	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded	Total (Excl Placebo)
6 – < 24 months	–	–	–	–	–	–	–	–	–	–	1164	1164
2 – < 6 years	–	–	–	–	–	–	–	–	–	–	1216	1216
6 – < 12 years	–	–	–	–	–	–	–	–	–	–	1260	1260
12 – < 18 years	75	–	–	–	2157	–	–	190	210	38	–	2595
18 – 34 years	1437	135	92	–	12 089	97	69	186	–	51	–	12 719
35 – 50 years	1938	143	143	52	13 930	113	122	225	–	103	31	14 862
51 – 65 years	2879	69	54	956	13 142	59	60	565	–	191	913	16 009
> 65 years	2131	–	8	414	5458	–	8	505	–	353	1875	8621
Total	8460	347	297	1422	46 776	269	259	1671	210	736	6459	58 446^a

^a Participants from the 2019nCoV-312 study (n = 147) are a subset of the participants in the 2019nCoV-307 study and are counted twice. Exposure data by specific age ranges are not available for Study 2019nCoV-415 and therefore are not presented.

Table 3 - Cumulative Participant Exposure Stratified by gender

Gender	Treatment/Number of Participants											
	Placebo	BA.1	BA.5	CIC	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded	Total (Excl Placebo)
Male	4343	155	133	586	24 235	118	120	698	103	359	3322	29 829

Gender	Treatment/Number of Participants											
	Placebo	BA.1	BA.5	CIC	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded	Total (Excl Placebo)
Female	4117	192	164	836	22 541	151	139	973	107	590	3137	28 830
Nonbinary	-	-	-	-	-	-	-	-	-	5	-	5
Prefer not to answer	-	-	-	-	-	-	-	-	-	1	-	1
Total	8460	347	297	1422	46 776	269	259	1 671	210	955	6459	58 665^a

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

Table 4 - Cumulative Participant Exposure Stratified by Race

Racial Group	Treatment/Number of Participants											
	Placebo	BA.1	BA.5	CIC	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded	Total (Excl Placebo)
Aboriginal Australian	–	–	–	1	3	–	–	–	–	–	5	9
African	–	–	–	–	–	–	–	–	–	–	2	2
American Indian or Alaska Native	199	–	–	2	1847	–	–	15	–	7	138	2009
Asian	314	48	39	43	1769	39	26	27	2	29	967	2989
Black or African American	598	1	16	–	7985	–	–	370	44	252	868	9536
Maori	–	–	–	14	2	–	–	–	–	–	44	60

Racial Group	Treatment/Number of Participants											
	Placebo	BA.1	BA.5	C19	Prototype	Prototype+BA.1	Prototype+BA.5	XBB.1.5	Prototype+XBB.1.5	JN.1	Blinded	Total (Excl Placebo)
Native Hawaiian or Other Pacific Islander	5	3	2	5	81	1	1	5	1	1	34	134
Southern African Coloured	–	–	–	–	–	–	–	–	–	–	1	1
White or Caucasian	7224	280	220	1314	33 886	220	215	1202	149	646	3137	41 269
Middle Eastern and/or North African	–	–	–	–	–	–	–	–	–	3	–	3
Other	12	10	14	17	149	8	14	8	2	2	1166	1390
Multiple	63	5	6	15	728	1	1	23	10	9	31	829
Missing or Not Reported	45	–	–	11	326	–	2	17	1	2	66	425
Unknown	–	–	–	–	–	–	–	4	1	4	–	9
Total	8460	347	297	1422	46 776	269	259	1671	210	955	6459	58 665^a

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

5.2 CUMULATIVE AND INTERVAL PATIENT EXPOSURE FROM MARKETING EXPERIENCE

5.2.1 Post-approval (non-clinical trial) exposure

Sanofi

There was no Sanofi sales data retrieved for the cumulative period (20 December 2021 to 19 December 2025) as well as for the interval period (20 December 2024 to 19 December 2025).

Partner Novavax

Sales figures for the interval period were received for the period from 20 December 2024 to 19 December 2025. Exposure from the cumulative experience is available from 20 December 2021 to 19 December 2025².

Interval sales

The total doses distributed during the interval period for Nuvaxovid JN.1 is 2 567 000. No doses were distributed for Nuvaxovid and Nuvaxovid XBB.1.5 during the interval period.

Cumulative sales

The total doses distributed during the cumulative period for Nuvaxovid is 104 284 800, for Nuvaxovid XBB.1.5 is 18 134 270, and for Nuvaxovid JN.1 is 5 914 840.

Overall doses distributed (Sanofi and Partner Novavax)

Based on the sales figure available from Sanofi and partner Novavax, the overall COVID-19 vaccine doses distributed during the cumulative period is estimated to be 128 333 910 and the overall COVID-19 vaccine doses distributed during the interval period is estimated to be 2 567 000.

Interval and Cumulative patient exposures are presented in [Appendix 5.2.1](#) and [Appendix 5.2.2](#), respectively.

5.2.2 Post-approval use in special populations

The MAH does not have access to cumulative exposure regarding use in special populations from the IBD of COVID-19 vaccine through the DLP of the PBRER.

² The distribution data provided includes all distribution since the IBD (20-Dec-2021) till 19-Dec-2025. The first Novavax commercial shipment was in February 2022, and there have been no additional shipments since November 2025.

Use in pregnancy and while breastfeeding; Use in immunocompromised patients; Use in frail patients with comorbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders); Use in patients with autoimmune or inflammatory disorders have been considered as missing information for COVID-19 vaccine. Please refer to Section 16 for further information.

5.2.3 Other post-approval use

No patterns of use with COVID-19 vaccine beyond that recommended in the reference product information, including overdose, drug abuse and misuse considered relevant for the interpretation of safety data were identified.

6 DATA IN SUMMARY TABULATIONS

The MAH routinely screens multiple data sources to identify new safety information on COVID-19 vaccine in addition to the review of the summary tabulations appended to this PBRER. Data sources routinely screened to identify relevant new safety information are listed in Section 15, Overview of Signals: new, ongoing or closed.

6.1 REFERENCE INFORMATION

The Medical Dictionary for Regulatory Activities (MedDRA) version 28.1 was used for the coding of adverse events (AEs) and adverse drug reactions (ADRs) and for analyses based on Standardized MedDRA Query (SMQ).

6.2 CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

[Appendix 2.1](#) provides the cumulative tabulation of serious adverse events (SAEs) reported from MAH-sponsored, interventional clinical trials where COVID-19 vaccine was the product under investigation.

The cumulative SAE tabulation is presented by treatment arm for completed or unblinded trials and blinded for ongoing blinded trials.

A total of 2987 cumulative SAEs were reported from MAH-sponsored clinical trials.

[Appendix 2.1](#) reflects the SAE data from the clinical trials reported in Section 5.1 that have been migrated into the PV database.

6.3 CUMULATIVE AND INTERVAL SUMMARY TABULATIONS FROM POSTMARKETING DATA SOURCES

The tabulation in [Appendix 2.2](#) includes:

- Serious and non-serious ADRs from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and Regulatory Authorities;
- Serious adverse reactions from non-interventional studies and
- Solicited reports of serious adverse reactions.³

As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported AEs imply suspicion of causality by the reporter and are therefore considered to be adverse reactions for regulatory reporting purposes.

The non-interventional postmarketing study and reports from other solicited sources data includes serious ADRs from interventional clinical trials in which COVID-19 vaccine was used as comparator, additional study drug.

A total of 21 792 cumulative adverse reactions have been reported for COVID-19 vaccine, 1824 of which were reported during the present reporting period (see [Appendix 2.2.1](#)).

A total of 254 cumulative adverse reactions have been reported for unknown manufacturer COVID-19 vaccines, of which 51 were reported during the present reporting period (see [Appendix 2.2.2](#)).

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

During the reporting interval of this PBRER, one clinical trial has been completed. In addition, one clinical trial concluded (ie, a final CSR was approved) during the previous reporting period but was erroneously considered and reported as ongoing. As of 19 December 2025 (DLP), a total of four clinical trials are ongoing.

A listing of all MAH-sponsored interventional trials completed or ongoing during the reporting period and with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of COVID-19 vaccine is presented in [Appendix 4.1](#).

³ Does not include data from MAH-sponsored interventional trials included in [Appendix 2.1](#).

7.1 COMPLETED CLINICAL TRIALS

As of the DLP for this PBRER (19 December 2025), the following clinical trial was completed (ie, a final CSR was approved): Study 2019nCoV-315 safety and immunogenicity of an Omicron JN.1 subvariant vaccine. No new clinically important safety or efficacy information emerged from this trial during the reporting interval.

The following clinical trial concluded (ie, a final CSR was approved) during the previous reporting period but was erroneously considered and reported as ongoing: Study 2019nCoV-205 High Dose SARS-CoV-2rS Vaccines Booster. No new clinically important safety or efficacy information emerged from this trial during either the previous or current reporting interval.

7.1.1 Efficacy findings

There were no clinically important emerging efficacy findings in studies completed during the reporting interval.

7.1.2 Safety findings

There were no clinically important emerging safety findings in studies completed during the reporting interval.

7.2 ONGOING CLINICAL TRIALS

As of the DLP for this PBRER (19 December 2025), the following clinical trials were ongoing (ie, final CSRs were not prepared): Study 2019nCoV-503, Study 2019nCoV-318 (Sanofi VBV23344), Study 2019nCoV-420, and Study 2019nCoV-415. During the PBRER reporting interval, no interim analyses were planned or conducted for any of the ongoing clinical trials.

There was no new clinically important information arising from studies ongoing during the reporting interval.

7.3 LONG-TERM FOLLOW-UP

Not applicable since there were no long-term follow-up programs or studies during the reporting interval.

7.4 OTHER THERAPEUTIC USE OF MEDICINAL PRODUCT

Not applicable; no expanded access programs, compassionate use programs, particular patient use, single patient Investigational New Drugs (INDs) or treatment INDs were ongoing or completed during the reporting interval.

7.5 NEW SAFETY DATA RELATED TO FIXED COMBINATION THERAPIES

Not applicable since the development program does not include a fixed combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

There were no safety or efficacy findings relevant to the benefit-risk assessment identified from non-interventional studies during the reporting interval.

During the reporting interval, three Post-Authorization Safety Studies (PASS) and three Post-Authorization Efficacy Studies (PAES) were ongoing. No MAH-sponsored non-interventional studies were completed during the reporting interval. There was also one collaborative research PAES study (BEEHIVE) ongoing during the reporting interval.

A listing of all MAH-sponsored non-interventional studies completed or ongoing during the reporting period, and with the primary aim of identifying, characterizing, quantifying a safety hazard, confirming the safety profile of COVID-19 vaccine, or measuring the effectiveness of risk management measures is presented in [Appendix 4.2](#).

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 OTHER CLINICAL TRIALS

Not applicable as no other clinical trial/study were ongoing or completed during the reporting period.

9.2 MEDICATION ERRORS

Medication Error coding in the Sanofi global PV database follows MedDRA introductory guide & MedDRA Term Selection - Points to Consider.

Events are coded in the global PV database utilizing the medication error Preferred Terms (PTs) as reported and assessed against the locally approved product information.

The MAH routinely screens multiple data sources to identify new safety information on medication errors. Data sources routinely screened to identify relevant new safety information are listed in Section 15.

Refer to [Appendix 6.2.1](#) for the numbers of PTs in the broad MedDRA SMQ “*Medication errors*” reported with or without serious or non-serious adverse reactions from post-authorization sources for COVID-19 vaccine. Refer to [Appendix 6.2.2](#) for the numbers of PTs in the broad MedDRA SMQ “*Medication errors*” reported with or without serious or non-serious adverse reactions from post-authorization sources for unknown manufacturer COVID-19 vaccines. [Appendix 6.2.1](#) and [Appendix 6.2.2](#) complies with the expectations defined in Table A2 1 in the good practice guide on recording, coding, reporting and assessment of medication errors.

A total of 52 cases were associated with medication errors during the reporting interval.

Cases with Nuvaxovid:

A total of eight cases of medication error were reported during the review period out of which three cases were serious and five cases were non-serious (two males, five females and one individual of unspecified gender with age range 27 years to 90 years when reported). These cases included eight AEs related to medication error which were coded to PTs: *Accidental overdose* (n = 3), *Incorrect dose administered* (n = 1), *Interchange of vaccine products* (n = 1), *Incomplete course of vaccination* (n = 1), *Incorrect route of product administration* (n = 1) and *Inappropriate schedule of product administration* (n = 1). In serious cases, the reported AEs were not related to medication error. In non-serious cases, no AEs were reported following medication error.

Cases with Nuvaxovid XBB.1.5:

A total of two cases of medication error were reported during the review period out of which one case was serious and one case was non-serious (two females aged 23 years and 44 years, respectively). These cases included two AEs related to medication error which were coded to PT: *Incomplete course of vaccination* (n = 2). In these cases, the reported AEs were not related to medication error.

Cases with Nuvaxovid JN.1:

A total of 40 cases of medication error were reported during the review period out of which one case was serious and 39 cases were non-serious (14 males, 19 females and seven individuals of unspecified gender with age range five years to 93 years when reported). These cases included 41 AEs related to medication error which were coded to PTs: *Expired product administered* (n = 16), *Incorrect route of product administration* (n = 8), *Incomplete course of vaccination* (n = 7), *Incorrect dose administered* (n = 2), *Circumstance or information capable of leading to medication error* (n = 1), *Intercepted product storage error* (n = 1), *Needle issue* (n = 1), *Product administered at inappropriate site* (n = 1), *Product administered to patient of inappropriate age* (n = 1), *Product administration error* (n = 1), *Product dose omission issue* (n = 1) and *Product use issue* (n = 1). In one serious case, the patient experienced pain and tendon injury as the tendon had been injected through during vaccination

resulting in a hole. The event was managed through surgery. In 35 non-serious cases, no AEs were reported following medication error. In the remaining four cases, the reported AEs were not related to medication error.

Unknown manufacturer COVID-19 vaccines:

A total of two non-serious cases of medication error were reported during the review period (two females aged 55 years and 83 years, respectively). These cases included two AEs related to medication error which were coded to PT: *Extra dose administered* (n = 1) and *Accidental exposure to product* (n = 1). In one case, the reported AEs were not related to medication error while in another case, no AEs were reported following medication error.

There were no relevant safety findings on patterns of medication errors and potential medication errors identified which would require specific risk minimization measures (RMMs) at this time. The information on patterns of medication errors and potential medication errors does not change the overall benefit-risk evaluation of COVID-19 vaccine.

No published significant safety findings regarding medication errors have been available during the reporting interval.

10 NON-CLINICAL DATA

No significant findings have been identified during the reporting interval.

11 LITERATURE

This section summarizes new and significant safety findings from literature relevant to COVID-19 vaccine that the MAH became aware of during the reporting interval.

Records identified are reviewed for periodic report inclusion using the criteria below:

- Publications describing non-case safety topics for Sanofi products
- Publications describing medication error, misuse, abuse or overdose (acute or chronic)
- Publications describing lack of efficacy
- Publications describing off-label use with safety impact
- Publications describing unlisted interactions or new data on listed interactions
- Publications reporting pregnancy or drug exposure via parent events (regardless of outcome, even if a normal outcome)

- Publications describing medically important safety information in a special population (not in the target population) that is not described in the product information
- Publications related to Adverse Events of Special Interests (AESIs) for vaccines implying an increased risk following vaccination or demonstrating no association between the AESI and the vaccine.
- Publications including non-clinical data related to safety, such as in vitro studies and animal studies
- Publications including clinical data related to safety, such as pharmacokinetic studies

During the reporting period, one publication containing new and significant safety findings was identified in the scientific (including non-clinical) and medical literature.

Mackenzie LJ, Bousie JA, Newman P, Cunningham J, Woodward AP, Silk-Jones J, et al. What three years of COVID-19 vaccine administration reveals about the incidence of shoulder injury related to vaccine administration (SIRVA). Vaccine. 2025 Apr 2;51:126892. (1)

Background

Shoulder injury related to vaccine administration (SIRVA) has been reported to be a rare but real complication of vaccination. It is considered attributable to an incorrect vaccine administration technique by the vaccinator. To date, evidence about SIRVA is mainly limited to case studies and case series, and the incidence remains unknown. This study aimed to determine the incidence of SIRVA.

Methods

The authors conducted a retrospective study of the publicly available Eudravigilance database (PV data). The authors examined all COVID-19 vaccine case reports administered between January 2020 and December 2022. The reports were analyzed to see if they met the Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) definition and inclusion criteria for SIRVA.

Results

Between January 2020, and December 2022, from 1 172 583 008 administered COVID-19 vaccines, 43 192 cases met the SAEFVIC inclusion criteria for SIRVA. This equals an incidence of 3.7 cases per 100 000 vaccines administered during the three years. Female subjects are disproportionately affected, with 33 828 cases (77.9 %). The incidence was higher with some COVID-19 vaccine formulations than others. By vaccine type, incidence ranged from 0.4 per 100 000 to 8 per 100 000 and it was lowest (0.4 per 100 000) for NVX-COV2373.

Conclusion

The incidence found in this study is higher than previously reported. The data also reflects that it affects more female subjects than males. While previously considered avoidable using the correct vaccine administration technique, the data challenges this notion as it shows that certain vaccine formulations may be associated with a higher incidence of the condition. The causes of SIRVA are likely multifaceted, with current understanding being further impacted by unclear definitions and reporting requirements.

MAH comment: *This study suggests that vaccine formulation (antigens and adjuvants) may also play a role in the development of SIRVA. However, potential confounding factors such as country of administration, levels of training of immunizers, and patient characteristics may be important considerations, and preclude interpretation of these estimates as direct effects. Case-level data, including for controls, would be required for further evaluation of these effects, perhaps via case-control design. Female subjects have been demonstrated to mount higher immunological responses to vaccination due to sex-linked immune response genes, which may explain the higher rates of SIRVA in female subjects. Overall, knowledge and understanding of SIRVA is largely hampered by a lack of uniform definitions, and poor reporting frameworks. The MAH will continue to monitor the cases of SIRVA through routine PV activities.*

12 OTHER PERIODIC REPORTS

The COVID-19 vaccine is not available as FDC. During the reporting interval, this is the only PBRER prepared by the MAH for this product.

No other periodic reports prepared by contractual partner for COVID-19 vaccine have been made available to the MAH during the reporting interval.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

No new controlled clinical trials indicating a lack of efficacy of COVID-19 vaccine in the authorized indications, relevant for the benefit-risk evaluation were identified during the reporting interval.

14 LATE-BREAKING INFORMATION

No new information regarding potentially important safety or efficacy and/or effectiveness pertaining to COVID-19 vaccine arose since the DLP for this PBRER.

15 OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

There were no signals that were ongoing at the DLP or closed during the reporting interval for COVID-19 vaccine. Therefore, [Appendix 3](#) is not applicable.

The sources routinely screened to identify relevant new safety information include:

- Global PV database, to identify signals from ICSRs and clusters of cases as well as from aggregate reports
- Scientific literature to identify signals from case reports or case series, published studies, meta-analyses
- Data mining in Eudravigilance database (when the product is included in the *Eudravigilance data mining pilot*)
- Product complaints database
- Regulatory Authority websites

The following sources of routine safety surveillance are also taken into consideration, as applicable:

- Safety queries and requests from Regulatory Authorities
- Clinical trials and other studies in human (individual study data and integrated study data), Independent Data Monitoring Committee reports
- Non-clinical safety information (ie, toxicology, safety pharmacology, pharmacokinetic data, in vitro studies)
- Pharmacoepidemiology studies, registries or other observational studies, analysis of pre-existing data
- Manufacturing site quality systems review
- Competitive intelligence
- Signals identified by partners
- Queries and requests from Ethics Committees, Institutional Review Boards
- Media (eg, press, television, internet including social media)

Depending on the source screened for signal detection and product-specific criteria, the following signal detection methods are used to identify new drug-event combinations, or an increased reporting of an event or a group of events, requiring further evaluation:

- Qualitative: Manual medical review of ICSRs recorded in the global PV database, and review of aggregate data to detect any new relevant AEs or a change in nature, and/or increased severity of a known ADR, with a particular focus on increased trends in reporting, newly reported events, and medication errors, non-case literature review.

- Semi-quantitative: Manual review of aggregate data from internal databases (eg, PV or Product Complaints database) such as event counts and frequency or proportion thresholds, sorting, and cross-tabulations, based on thresholds, evaluation algorithms and medical judgment.

15.1 TOPICS REQUESTED BY A REGULATORY AUTHORITY TO BE MONITORED IN THE PBRER

As in all PBRERs and although there was no signal, all cases with a fatal outcome and vaccination failure were reviewed during the period. The results of this analysis are provided below.

Fatal cases

A total of 17 cases with fatal outcome were reported during the review period. These cases are described below.

Cases with Nuvaxovid:

Nine cases with fatal outcome were reported during the review period (seven males and two females with age range 26 years to 100 years). These nine cases included 23 fatal AEs coded to PTs: *Hypersensitivity* (n = 4), *Pyrexia* (n = 2), *Headache* (n = 2), *Dyspnoea* (n = 2), *Urticaria* (n = 2), *Rash* (n = 2), *Shock haemorrhagic* (n = 1), *Coronary artery thrombosis* (n = 1), *Sudden death* (n = 1), *Gastric cancer* (n = 1), *Metastasis to liver* (n = 1), *Adverse event* (n = 1), *Cardiovascular disorder* (n = 1), *Acute respiratory failure* (n = 1) and *Death* (n = 1).

In two of these nine cases, the patient's medical history of chronic cardiac failure, aortic aneurysm and renal disorder can be considered as confounding factors for the reported fatal AEs. In one case, the reported event onset latency was more than two years hence, the causal association with vaccination can be excluded. In the remaining six cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid XBB.1.5:

Four cases with fatal outcome were reported during the review period (two females, one male and one individual of unknown gender with age range 55 years to 92 years). These four cases included 11 fatal AEs coded to PTs: *Myocardial infarction* (n = 1), *Syncope* (n = 1), *Respiratory failure* (n = 1), *Cardiac arrest* (n = 1), *Death* (n = 1), *Sudden death* (n = 1), *Dyspnoea* (n = 1), *Blood pressure decreased* (n = 1), *Oxygen saturation decreased* (n = 1), *Asthenia* (n = 1) and *Pyrexia* (n = 1).

In three of these four cases, the patient's medical history of diabetes mellitus (DM), hypertension, atherosclerosis in the lower limbs, myocardial infarction, hypersensitivity, chronic kidney disease stage 4, atrial fibrillation, angina pectoris, kidney cancer, hypercholesterolemia, COPD, recent contact with the persons tested positive for COVID-19 can be considered as confounding factors for the

reported fatal AEs. In the remaining one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid JN.1:

Three cases with fatal outcome were reported during the review period (two females and one male with age range 71 years to 88 years). These three cases included three fatal AEs coded to PTs: *Myocardial infarction* (n = 1), *Cardiovascular disorder* (n = 1) and *Gastrointestinal haemorrhage* (n = 1).

In two of these three cases, the patient's medical history of hypertension, atrial fibrillation, pulmonary hypertension and concomitant medication warfarin can be considered as confounding factors for the reported fatal AEs. In the remaining one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Unknown manufacturer COVID-19 vaccines:

One case was reported in a 67-year-old female patient during the review period. In this case, there is a limited information regarding the medical history, medical condition at the time of vaccination, event onset latency, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Overall, no new safety concern was identified following the evaluation of fatal case reports.

Vaccination failure

A search to retrieve all postmarketing cases of vaccination failure or vaccination failure related conditions (MedDRA [version 28.1] SMQ Broad: "*Lack of efficacy/effect*") both medically confirmed and unconfirmed reported during the reporting period for COVID-19 vaccine was performed in the Sanofi global PV Database.

The vaccination failure is defined if the below three criteria, as recommended in "Detailed Guidance on ICSRs in the context of COVID-19" provided by the European Medicines Agency (07 April 2022), are met:

1. Associated COVID-19 symptoms are reported.
2. The reported events occur after the normal time period for the protection to be acquired as a result of immunization in line with the suspected vaccine product information. This time period is defined as seven or more days past the date of the second vaccination, or booster administration.
3. A positive diagnostic test for COVID-19 is also reported in the case.

A total of 10 cases retrieved for evaluation of vaccination failure were analyzed during the reporting period. These cases are described below.

Cases with Nuvaxovid:

Two cases were retrieved during this review period. These cases were reported in male patient aged 27 years and female patient aged 41 years, respectively. The reported PTs related to vaccination failure were: *Vaccination failure* (n = 1), *Drug ineffective* (n = 1) and *COVID-19* (n = 2). Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and disability or permanent damage (n = 1).

In these cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 150 days to 182 days. In one case, the patient had medical history of infection susceptibility increased which can be considered as confounding factor for COVID-19 infection hence, it is not considered as a case of true vaccination failure. In the remaining case, the reported laboratory investigations and clinical examination following COVID-19 infection were normal.

The reported case outcomes were: not recovered/not resolved (n = 1) and unknown (n = 1).

Cases with Nuvaxovid XBB.1.5:

Two cases were retrieved during this review period. These cases were reported in females aged 64 years and 69 years, respectively. The reported PTs related to vaccination failure were: *Vaccination failure* (n = 2) and *COVID-19* (n = 2). Both the cases were serious due to medically significant criteria (n = 2) and disability or permanent damage (n = 1).

In these cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 25 days to 326 days. In one case, the patient had medical history of allergic asthma which can be considered as confounding factor for COVID-19 infection hence, it is not considered as a case of true vaccination failure. In the remaining case, the patient had medical history of COVID-19 infection twice before the vaccination with Nuvaxovid XBB.1.5. However, no additional information regarding clinical course and other laboratory investigations was reported hence, further assessment was not possible.

The reported case outcomes were: recovered/resolved (n = 1) and recovered/resolved with sequelae (n = 1).

Cases with Nuvaxovid JN.1:

Five cases were retrieved during this review period. All the cases were reported in females with age range of 24 years to 56 years. The reported PTs related to vaccination failure were: *Vaccination failure* (n = 3), *Breakthrough COVID-19* (n = 2), *Drug ineffective* (n = 2), *COVID-19* (n = 2) and *Coronavirus infection* (n = 1). All the cases were serious due to medically significant criteria.

In one case, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course, event onset latency, laboratory investigations hence, the role of the suspect vaccine could not be assessed. In the remaining four cases, the infection with COVID-19 was confirmed by laboratory tests and the event onset latency for COVID-19 infection ranged from 34 days to 88 days. In three of these four cases, the patients had medical history of hypogammaglobulinemia, breast carcinoma and cough variant asthma which can be considered as confounding factors for COVID-19 infection hence, they are not considered as cases of true vaccination failure. In the remaining case, the reported laboratory investigations and clinical examination following COVID-19 infection were normal.

The reported case outcomes were: recovered/resolved (n = 4) and recovered/resolved with sequelae (n = 1).

Unknown manufacturer COVID-19 vaccines:

One case was reported during the review period. In this case, the PT of *Drug ineffective* was reported with dupilumab and not with COVID-19 vaccine.

Based on the available information, no significant safety concern is identified. It is to be noted that as with any vaccine, vaccination with COVID-19 vaccine may not protect 100% of susceptible individuals.

New relevant efficacy and/or effectiveness or vaccine failure findings from published clinical studies performed in authorized indications made available during the reporting interval are further discussed in Section 17.2.

16 SIGNAL AND RISK EVALUATION

16.1 SUMMARY OF SAFETY CONCERNS

A summary of the safety concerns for COVID-19 vaccine identified at the beginning of the reporting interval is presented in Table 5.

Table 5 - Summary of safety concerns at the beginning of the reporting interval

Important identified risks	- Myocarditis and/or pericarditis^{a,b} - Anaphylaxis^b
Important potential risks	- Vaccine associated enhanced disease, including VAERD^a - Atrial fibrillation and/or Atrial flutter^b - Cerebrovascular Accident^b

	• Cranial Nerve VIII Disorders (including Vestibular Neuronitis)^b • Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)^b
Missing information	• Use in pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interaction with other vaccines • Long-term safety

^a Important identified risk and important potential risk as per the current EU-RMP version 7.1 dated 25-Feb-2025.

^b Important identified risk and important potential risks per the current US PV plan version 3.6 dated 25-Mar-2025.

COPD: Chronic Obstructive Pulmonary Disease; VAERD: Vaccine Associated Enhanced Respiratory Disease; EU: European Union; RMP: Risk Management Plan; US: United States; PV: Pharmacovigilance.

16.2 SIGNAL EVALUATION

For an overview of all ongoing and closed signals refer to Section 15. This sub-section summarizes the results of evaluations of all signals closed during the interval period. Important identified and potential risks are characterized in Section 16.4.

16.2.1 Signals categorized as a potential or identified risk

There were no signals that were closed and adjudicated either as potential or identified risk during the reporting period for COVID-19 vaccine. Therefore, Appendix 5.3 is not applicable.

16.2.2 Signals adjudicated as not a safety issue

There were no signals adjudicated as not a safety issue during the reporting period for COVID-19 vaccine. Therefore, Appendix 5.3 is not applicable.

16.3 EVALUATION OF RISKS AND NEW INFORMATION

16.3.1 New information on important potential risks

Utilizing the surveillance activities defined in Section 15, the MAH has determined that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized important potential risk. However, details regarding the new relevant safety information are included below.

Vaccine associated enhanced disease, including VAERD

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** 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 Vaccine Associated Enhanced Disease (VAED)/VAERD.

The VAED/VAERD, if it would occur in vaccinated persons, would manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (eg, older or immunocompromised, immunocompromised children, and children with chronic conditions) having higher rates of fatal outcomes, or for observation of an unfavorable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated.

- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) PTs: *Antibody-dependent enhancement* and *Enhanced respiratory disease*.
- **Results:** During the review period, no new cases of VAED, including VAERD were retrieved for COVID-19 vaccine.

Unknown manufacturer COVID-19 vaccines:

In addition, no cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.

- **Discussion:** Cumulatively, there are seven case reports (all serious) retrieved with the above-mentioned search.

The reporting rate of VAED, including VAERD remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of VAED, including VAERD. The MAH will continue to monitor this important potential risk in the future PBRERs.

Atrial Fibrillation and/or Atrial Flutter

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Atrial fibrillation and/or atrial flutter have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.

- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) PTs: *Atrial fibrillation* and *Atrial flutter*.
- **Results:** During the review period, eight new cases of atrial fibrillation and/or atrial flutter were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Five cases of atrial fibrillation and/or atrial flutter were retrieved during the review period (all males with age range 45 years to 64 years). The reported PTs in these cases were as following: *Atrial fibrillation* (n = 5) and *Atrial flutter* (n = 1). All the cases were serious due to hospitalization (n = 3) and medically significant criteria (n = 5). The reported case outcomes were: not recovered/not resolved (n = 1), recovered/resolved (n = 2), recovering/resolving (n = 1) and unknown (n = 1). In two cases, the event of atrial fibrillation and/or atrial flutter can be confounded by concomitant medications amlodipine/olmesartan and tamsulosin; and the patient's ongoing medical condition of mitral valve incompetence, respectively. In one case, the event of atrial fibrillation was reported following myocarditis (the case met Level 2 Brighton Collaboration [BC] case definition for myocarditis). In the remaining two cases, the reported event onset latencies were 235 days and; 10 months and 24 days, respectively hence, the causal role of the suspect vaccine can be excluded.

Cases with Nuvaxovid XBB.1.5:

One case of atrial fibrillation and/or atrial flutter was retrieved in 55-year-old male patient during the review period. The reported PT was *Atrial fibrillation* (n = 1). The case was serious due to hospitalization and medically significant criteria. The reported case outcome was recovering/resolving. The reported event can be confounded by the co-suspect medication peginterferon alfa-2a.

Cases with Nuvaxovid JN.1:

Two cases of atrial fibrillation and/or atrial flutter were retrieved during the review period (one male aged 67 years and one female aged 54 years). In both cases, the PT of *Atrial fibrillation* (n = 2) was reported. Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and life threatening (n = 1). The reported case outcome was recovered/resolved in both the cases. In both the cases, limited information was available regarding the clinical course, medical history and medical condition at the time of vaccination hence, the role of the suspect vaccine could not be assessed.

Unknown manufacturer COVID-19 vaccines:

No new cases of atrial fibrillation and/or atrial flutter were retrieved during the review period.

- **Discussion:** Cumulatively, there are 29 case reports (26 serious and three non-serious) retrieved with the above-mentioned search.

The reporting rate of atrial fibrillation and/or atrial flutter remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of atrial fibrillation and/or atrial flutter. The MAH will continue to monitor this important potential risk in the future PBRERs.

Cerebrovascular Accident

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Cerebrovascular accident has been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) SMQs (Narrow): *Haemorrhagic central nervous system vascular conditions* and *Ischaemic central nervous system vascular conditions*.
- **Results:** During the review period, 10 new cases of cerebrovascular accident were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Seven cases of cerebrovascular accident were retrieved during the review period (three males and four females with age range 20 years to 74 years). The reported PTs in these cases were as following: *Brain stem infarction* (n = 1), *Cerebrovascular accident* (n = 4), *Ischemic stroke* (n = 1), *Cerebral infarction* (n = 1) and *Transient ischemic attack* (n = 1). All the cases were serious due to disability/permanent damage (n = 1), hospitalization (n = 7) and medically significant criteria (n = 6). The reported case outcomes were: not recovered/not resolved (n = 3), recovered/resolved with sequelae (n = 2), recovered/resolved (n = 1) and recovering/resolving (n = 1). In one case, the patient had medical history of cerebral small vessel ischemic disease which can be considered as confounding factor for cerebrovascular accident. In the remaining cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid XBB.1.5:

Two cases of cerebrovascular accident were retrieved during the review period (one male aged 32 years and one female aged 82 years). The reported PTs in these cases were as following: *Ischemic stroke* (n = 1) and *Thalamic infarction* (n = 1). Both the cases were serious due to hospitalization (n = 1) and medically significant criteria (n = 2). In both the cases, the reported case outcome was unknown. In these cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed.

Cases with Nuvaxovid JN.1:

One case of cerebrovascular accident was retrieved in an 80-year-old male patient during the review period. In this case, the PT of *Cerebrovascular accident* (n = 1) was reported. The case was serious due to hospitalization, life threatening, disability/permanent damage and medically significant criteria. The reported case outcome was unknown. In this case, the reported event can be confounded by ongoing medical conditions of arrhythmia, hypertension, hydrocephalus and dementia.

Unknown manufacturer COVID-19 vaccines:

No new cases of cerebrovascular accident were retrieved during the review period.

- **Discussion:** Cumulatively, there are 24 case reports (all serious) retrieved with the above-mentioned search.

The reporting rate of cerebrovascular accident remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of cerebrovascular accident. The MAH will continue to monitor this important potential risk in the future PBRERs.

Cranial Nerve VIII Disorders (including Vestibular Neuronitis)

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Cranial nerve VIII disorders (including vestibular neuronitis) have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) High Level Term (HLT): *VIIIth cranial nerve disorders*.
- **Results:** During the review period, no new cases of cranial nerve VIII disorders (including vestibular neuronitis) were retrieved for COVID-19 vaccine.

In addition, no new cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.

- **Discussion:** Cumulatively, no cases of cranial nerve VIII disorders (including vestibular neuronitis) were retrieved for COVID-19 vaccine.
- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of cranial nerve VIII disorders (including vestibular neuronitis). The MAH will continue to monitor this important potential risk in the future PBRERs.

Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) have been considered as an important potential risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025.
- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) HLT: *Eye movement disorders*.
- **Results:** During the review period, no new cases of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) were retrieved for COVID-19 vaccine.

Unknown manufacturer COVID-19 vaccines:

In addition, no new cases were retrieved for unknown manufacturer COVID-19 vaccines during the review period.

- **Discussion:** Cumulatively, there is one serious case report retrieved with the above-mentioned search.

The reporting rate of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI). The MAH will continue to monitor this important potential risk in the future PBRERs.

16.3.2 New information on important identified risks

Utilizing the surveillance activities defined in Section 15, the MAH has determined that there was no new relevant safety information that would have an impact on the understanding and characterization of the previously recognized important identified risk. However, details regarding the new relevant safety information are included below.

Myocarditis and/or pericarditis

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Myocarditis and pericarditis have been reported in male and female adults within 14 days of administering COVID-19 vaccine.

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for MedDRA (version 28.1) SMQ (broad): *Non-infectious myocarditis/pericarditis*; HLTs: *Infectious myocarditis*, *Infectious pericarditis*, *Non-infectious myocarditis*, *Non-infectious pericarditis*.
- **Results:** During the review period, 48 new cases of myocarditis and/or pericarditis were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Forty (40) cases were retrieved for evaluation of myocarditis and/or pericarditis which were analyzed during the review period (16 males and 24 females with age range 18 years to 90 years when reported). These 40 cases included 45 AEs reported to PTs: *Atrioventricular block complete* (n = 1), *Bundle branch block left* (n = 1), *Cardiac failure* (n = 2), *Electrocardiogram abnormal* (n = 1), *Electrocardiogram change* (n = 1), *Extrasystoles* (n = 6), *Left ventricular failure* (n = 2), *Myocarditis* (n = 6), *Myopericarditis* (n = 4), *Pericardial effusion* (n = 3), *Pericarditis* (n = 8), *Red blood cell sedimentation rate increased* (n = 2), *Right ventricular failure* (n = 1), *Sudden death* (n = 1), *Supraventricular tachycardia* (n = 1), *Tachyarrhythmia* (n = 2), *Tachycardia paroxysmal* (n = 1) and *Ventricular extrasystoles* (n = 2). Thirty-five (35) cases were serious due to death (n = 1), life-threatening (n = 3), hospitalization (n = 16) and medically significant criteria (n = 33). The reported case outcomes were: fatal (n = 1), not recovered/not resolved (n = 13), recovered/resolved with sequelae (n = 2), recovered/resolved (n = 5), recovering/resolving (n = 8) and unknown (n = 11). Thirty-four (34) out of these 40 cases do not meet Level 1 – 3 BC case definitions for myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis. Five cases met Level – 2, and one case met Level – 1 BC case definitions for myocarditis and/or pericarditis.

Cases with Nuvaxovid XBB.1.5:

Six cases retrieved for evaluation of myocarditis and /or pericarditis which were analyzed during the reporting period (two male and four females with age range 55 years to 91 years when reported). These six cases included six AEs reported to PTs: *Pericarditis* (n = 2), *Myopericarditis* (n = 1), *Extrasystoles* (n = 1), *Sudden death* (n = 1) and *Cardiac arrest* (n = 1). Five cases were serious due to death (n = 2), hospitalization (n = 4) and medically significant criteria (n = 5). The reported case outcomes were: fatal (n = 2), recovering/resolving (n = 2), recovered/resolved (n = 1) and not recovered/not resolved (n = 1). These cases do not meet Level 1 – 3 BC case definitions for myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis.

Cases with Nuvaxovid JN.1:

Two cases retrieved for evaluation of myocarditis and /or pericarditis which were analyzed during the reporting period (one male aged 67 years and one individual of unknown age and gender). These two cases included two AEs reported to PTs: *Pericardial effusion* (n = 1) and

Cardiac failure (n = 1). Both the cases were serious due to medically significant criteria (n = 2), hospitalization (n = 1) and life threatening (n = 1). The reported case outcomes were: recovered/resolved (n = 1) and unknown (n = 1). These cases do not meet Level 1 – 3 BC case definitions for myocarditis and/or pericarditis, hence, they are not considered as cases of myocarditis and/or pericarditis.

Unknown manufacturer COVID-19 vaccines:

No new cases of myocarditis and/or pericarditis were retrieved during the review period.

- **Discussion:** Cumulatively, there are 167 case reports (139 serious and 28 non-serious) retrieved with the above-mentioned search.

The reporting rate of myocarditis and/or pericarditis remains low and stable over time.

Myocarditis and/or pericarditis have been mentioned under the following sub-sections of CCDS (refer [Appendix 1](#)): ‘Special Warnings and Precautions for Use’ and ‘Undesirable Effects’ reported during postmarketing experience.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of myocarditis and/or pericarditis. The MAH will continue to monitor this important identified risk in the future PBRERs.

Anaphylaxis

- **Source of new information:** Cases retrieved during the review period from safety (global PV) database.
- **Background relevant to the evaluation:** Anaphylaxis has been considered as an important identified risk for COVID-19 vaccine as per US PV plan version 3.6 dated 25 March 2025 however, it is a non-important identified risk as per the current EU-RMP version 7.1 dated 25 February 2025.
- **Method(s) of evaluation, including data sources, search criteria, and analytical approaches:** The safety (global PV) database was searched for *Anaphylactic reaction algorithmic* SMQ.
- **Results:** During the review period, 24 new cases of anaphylaxis were retrieved for COVID-19 vaccine.

Cases with Nuvaxovid:

Twenty (20) cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (three males and 17 females with age range 23 years to 81 years). The reported PTs in these cases were as following: *Circulatory collapse* (n = 5), *Rash* (n = 8), *Angioedema* (n = 1), *Anaphylactic reaction* (n = 4), *Anaphylactic shock* (n = 3), *Hypersensitivity* (n = 5), *Loss of consciousness* (n = 4), *Hypotension* (n = 1), *Erythema* (n = 2), *Pruritus* (n = 5), *Blood pressure decreased* (n = 1), *Swollen tongue* (n = 3), *Eye irritation* (n = 1), *Vomiting* (n = 1), *Ocular hyperaemia* (n = 1), *Eye swelling* (n = 1), *Cyanosis* (n = 1), *Lip oedema* (n = 1), *Cough*

(n = 1), *Rhinorrhoea* (n = 1) and *Urticaria* (n = 2). One case was non-serious while 19 cases were serious due to death (n = 2), life threatening (n = 2), disability/permanent damage (n = 1), hospitalization (n = 5) and medically significant criteria (n = 17). The reported case outcomes were: fatal (n = 2), not recovered/not resolved (n = 5), recovered/resolved with sequelae (n = 1), recovered/resolved (n = 9), recovering/resolving (n = 1) and unknown (n = 2).

In two fatal cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. These cases met Level – 4 of the BC case definition for anaphylaxis.

In six of the remaining 18 cases, the patients had medical history of hypersensitivity, allergic rhinitis and urticaria which can be considered as confounding factors for the reported events. In the remaining 12 cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. Overall, two cases met Level – 2, and six cases met Level – 4 of the BC case definition for anaphylaxis. The remaining cases were not considered as cases of anaphylaxis.

Cases with Nuvaxovid XBB.1.5:

Two cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (one male aged 92 years and one female aged 86 years). The reported PTs in these cases were as following: *Oxygen saturation decreased* (n = 2) and *Blood pressure decreased* (n = 1). Both the cases were serious due to death (n = 2), hospitalization (n = 1) and medically significant criteria (n = 1). In both the cases, the reported case outcome was fatal.

In these cases, the patients have medical history of hypertension, myocardial infarction, drug hypersensitivity, diabetes mellitus, arteriosclerosis, chronic obstructive pulmonary disease, hypercholesterolemia and dementia which can be considered as confounding factors for the reported events and fatal outcome. These cases do not meet the BC case definition for anaphylaxis hence, they are not considered as cases of anaphylaxis.

Cases with Nuvaxovid JN.1:

Two cases were retrieved for evaluation of anaphylaxis which were analyzed during the review period (one female aged 38 years and one elderly female of unknown age). The reported PTs in these cases were as following: *Oxygen saturation decreased* (n = 2), *Pruritus* (n = 1), *Urticaria* (n = 1), *Stridor* (n = 1), *Cough* (n = 1), *Swelling face* (n = 1), *Rash pruritic* (n = 1), *Rhinorrhoea* (n = 1) and *Swelling of eyelid* (n = 1). Both the cases were serious due to hospitalization (n = 1) and medically significant criteria (n = 2). The reported case outcomes were: not recovered/not resolved (n = 1) and recovered/resolved (n = 1). In these cases, there is a limited information regarding the medical history, medical condition at the time of vaccination, clinical course and laboratory investigations hence, the role of the suspect vaccine could not be assessed. These cases do not meet the BC case definition for anaphylaxis hence, they are not considered as cases of anaphylaxis.

Unknown manufacturer COVID-19 vaccines:

No new cases of anaphylaxis were reported during the review period.

- **Discussion:** Cumulatively, there are 176 case reports (106 serious and 70 non-serious) retrieved with the above-mentioned search.

The reporting rate of anaphylaxis remains low and stable over time.

- **Conclusion:** Based on this review, there is no new or significant safety information identified for COVID-19 vaccine and the risk of anaphylaxis. The MAH will continue to monitor this important identified risk in the future PBRERs.

16.3.3 New information on other potential risks not categorized as important

There are no potential risks not categorized as important for COVID-19 vaccine, therefore this section is not applicable.

16.3.4 New information on other identified risks not categorized as important

Utilizing the surveillance activities defined in Section 15, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of previously recognized identified risk not categorized as important or warrants further discussion in the PBRER.

Anaphylaxis is an identified risk for COVID-19 vaccine that is not categorized as important as per the current EU-RMP version 7.1 dated 25 February 2025 however, it is an important identified risk as per the US PV plan version 3.6 dated 25 March 2025. Please refer to Section 16.3.2 for further information related to this important identified risk.

16.3.5 Update on missing information

Utilizing the surveillance activities defined in Section 15, the MAH has not identified any new safety information during the reporting interval that would have an impact on the understanding and characterization of missing information or warrants further discussion in the PBRER.

16.4 CHARACTERIZATION OF RISKS

The MAH routinely screens multiple data sources to identify new safety information on the list of safety concerns. Data sources routinely screened to identify relevant new safety information are listed in Section 15. Any data received during the reporting interval that may change the current understanding of the risks are reported in Section 16.3.

A summary of the safety concerns for COVID-19 vaccine identified at the end of the reporting interval is presented in [Table 6](#).

Table 6 - Summary of safety concerns at the end of the reporting interval

Important identified risks	- Myocarditis and/or pericarditis^{a,b} - Anaphylaxis^b
Important potential risks	- Vaccine associated enhanced disease, including VAERD^a - Atrial fibrillation and/or Atrial flutter^b - Cerebrovascular Accident^b - Cranial Nerve VIII Disorders (including Vestibular Neuronitis)^b - Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)^b
Missing information	- Use in pregnancy and while breastfeeding - Use in immunocompromised patients - Use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders) - Use in patients with autoimmune or inflammatory disorders - Interaction with other vaccines - Long-term safety

^a Important identified risk and important potential risk as per the current EU-RMP version 7.1 dated 25-Feb-2025.

^b Important identified risk and important potential risks per the current US PV plan version 3.6 dated 25-Mar-2025.

COPD: Chronic Obstructive Pulmonary Disease; VAERD: Vaccine Associated Enhanced Respiratory Disease; EU: European Union; RMP: Risk Management Plan; US: United States; PV: Pharmacovigilance

16.4.1 Important identified and potential risks

Table 7 - Important identified risk: Myocarditis and/or pericarditis

Identified risk	Myocarditis and/or pericarditis
Potential mechanism(s)	A mechanism of action by which a vaccine could cause myocarditis and/or pericarditis has not been established. Myocarditis can be caused by a variety of infectious and non-infectious causes, with viruses being the most common pathogen. Other common causes include autoimmune disorders such as systemic lupus erythematosus. In the general population, the incidence of myocarditis is approximately between 10 to 20 cases per 100 000 persons per year. According to some estimates, 1 to 5% of all patients with acute viral infections may involve the myocardium. The majority of patients are young, healthy males. Individuals who are most susceptible to myocarditis include children, pregnant women, and those who are immunocompromised (2). Myocarditis begins with the direct invasion of an infectious agent and its subsequent replication within or around the myocardium causing myonecrosis. The subacute phase is defined by an

Identified risk	Myocarditis and/or pericarditis
	increase in autoimmune-mediated injury with activated T cells and B cells and subsequent antibody production creating cardiac autoantibodies along with inflammatory proteins (2).
Evidence source(s) and strength of evidence	Literature on COVID-19 vaccines, post-market safety data, and clinical trial data.
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) <i>Participants 12 years of age and older</i> In the placebo-controlled safety dataset for NVX-CoV2373 (ie, prior to blinded crossover) (2019nCoV-301 (Adults), 2019nCoV-301 (Adolescents), 2019nCoV-302, and 2019nCoV-101 Part 2), 30 058 subjects received active vaccine, and 19 892 subjects received placebo. Two cases of myocarditis were reported following exposure to NVX-CoV2373, and one case was reported following exposure to placebo. The myocarditis/pericarditis exposure adjusted incidence rate per 100 PY of 0.03 events/100 PY for NVX-CoV2373 compared to 0.02 events/100 PY for placebo with an adjusted risk difference of 0.00 (95%: -0.06, 0.07). In the post-crossover phase of the studies 301 and 302, three cases of myocarditis were reported including an adolescent participant. The observed rate of 3 cases/14 513 PY falls within the expected rate of 1.6 – 4.6 cases/14 513 PY as determined by the EU ACCESS study. Of note, the exposure adjusted incidence post-crossover is the same as the placebo incidence of 0.02 events/100 PY during the placebo-controlled period suggesting a stable background incidence rate. The Sponsor assessed the causality as not related for the five cases occurring after exposure to NVX-CoV2373; all cases were attributed to alternative etiologies, including reasonable infectious and/or non-infectious causes. There were no cases of myocarditis/pericarditis assessed as related by the Sponsor. There were no participants who reported a TEAE of myocarditis and/or pericarditis in completed studies 2019nCoV-101 Part 1, 2019nCoV-505, 2019nCoV-311 Parts 1 and 2, 2019nCoV-313 Parts 1 and 2, 2019nCoV-314, 2019nCoV-315; and ongoing studies 2019nCoV-318 (Sanofi VBV23344), and 2019nCoV-420. Postmarketing experience - Cumulatively, 167 cases were reported [search strategy: <i>Infectious myocarditis</i> (HLT), <i>Noninfectious myocarditis</i> (HLT), <i>Infectious pericarditis</i> (HLT), <i>Noninfectious pericarditis</i> (HLT), <i>Noninfectious myocarditis/pericarditis</i> (SMQ) (SMQ Broad)] till DLP 19-Dec-2025. - Postmarketing reporting rate: 0.13/100 000 doses distributed. - The reported PTs were <i>Atrioventricular block complete</i> [n = 1], <i>Bundle branch block left</i> [n = 2], <i>Cardiac arrest</i> [n = 2], <i>Cardiac death</i> [n = 1], <i>Cardiac failure</i> [n = 5], <i>Cardio-respiratory arrest</i> [n = 1], <i>Carditis</i> [n = 5], <i>Echocardiogram abnormal</i> [n = 5], <i>Ejection fraction decreased</i> [n = 2], <i>Electrocardiogram abnormal</i> [n = 15], <i>Electrocardiogram change</i> [n = 1], <i>Electrocardiogram ST segment abnormal</i> [n = 1], <i>Electrocardiogram T wave inversion</i> [n = 1], <i>Extrasystoles</i> [n = 17], <i>Left ventricular dysfunction</i> [n = 1], <i>Left ventricular failure</i> [n = 2], <i>Myocardial injury</i> [n = 1], <i>Myocarditis</i> [n = 28], <i>Myopericarditis</i> [n = 9], <i>Pericardial effusion</i> [n = 8], <i>Pericarditis</i> [n = 63], <i>Red blood cell sedimentation rate increased</i> [n = 2], <i>Right ventricular failure</i> [n = 1], <i>Sudden death</i> [n = 2], <i>Supraventricular extrasystoles</i> [n = 4], <i>Supraventricular tachycardia</i> [n = 3], <i>Tachyarrhythmia</i> [n = 2], <i>Tachycardia paroxysmal</i> [n = 1], <i>Troponin increased</i> [n = 8], <i>Ventricular extrasystoles</i> [n = 8], <i>Ventricular tachycardia</i> [n = 1]; [Total number of events = 203]. - Gender: Male = 77, Female = 87 and Unknown = 3 - Age range: 14 years to 91 years when age is reported

Identified risk	Myocarditis and/or pericarditis
	- Age group (when age is reported): Adolescent = 1 (Aged 14 years), Younger adults aged 18-25 years = 18, Adults aged >25 years = 113, Elderly = 20 - Serious events: n = 151 with seriousness criteria: Death = 5, Life threatening = 7, Caused/prolonged hospitalization = 51 and Other: medically important condition = 140 - Time to onset of event after the first dose: 0-7 days = 63, 8-14 days = 20, ≥15 days = 26, unknown = 94 - Event outcome at the time of reporting: Fatal = 5, No recovered/not resolved = 72, Recovered/resolved with sequelae = 3, Recovered/resolved = 21, Recovering/resolving = 17, Unknown = 85.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk (European Respiratory Virus Surveillance Summary 2024) (3). Immunocompromised patients may be at a higher risk.
Preventability	Routine RMMs in the form of product labelling are included in the EU SmPC.
Impact on the risk-benefit balance of the product	Balanced with the risk of death and illness (including myocarditis) seen with COVID-19 itself, the vaccine has a favorable risk-benefit balance.
Public health impact	As this event is limited to the individual patient and considering the low rates of myocarditis and/or pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) caused by COVID-19, the public health impact is considered minimal.

COVID-19: Coronavirus disease 2019; PY: Person Years; EU: European Union; TEAE: Treatment Emergent Adverse Event; SmPC: Summary of product Characteristics; PT: Preferred Term; DLP: Data Lock Point; SMQ: Standardized MedDRA Query; RMM: Risk Minimization Measure.

Table 8 - Important identified risk: Anaphylaxis

Identified risk	Anaphylaxis
Potential mechanism(s)	Although rare, anaphylaxis may be life-threatening as multiple organs of different systems may be acutely affected, including the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. The underlying mechanisms can be immunological, non-immunological (previously termed anaphylactoid reactions), or idiopathic, with all three types leading to a similar clinical picture (4).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data. The risk of anaphylaxis is idiosyncratic in nature, with anaphylaxis risk after all vaccines estimated to be 1.31 (95% CI, 0.90 – 1.84) per million vaccine doses (5).
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) One serious case of anaphylactic shock was reported from clinical sponsored studies. The event of Anaphylactic shock was considered as not related to study vaccine. Postmarketing experience (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) - Cumulatively, 176 cases were retrieved (Search strategy: Anaphylactic reaction algorithmic SMQ) till DLP 19-Dec-2025. - The reported PTs were <i>Anaphylactic reaction</i> [n = 52], <i>Anaphylactic shock</i> [n = 7], <i>Anaphylactoid reaction</i> [n = 24], <i>Angioedema</i> [n = 6], <i>Blood pressure decreased</i> [n = 2], <i>Blood</i>

Identified risk	Anaphylaxis
	<i>pressure systolic decreased</i> [n = 1], <i>Circulatory collapse</i> [n = 5], <i>Cough</i> [n = 15], <i>Cyanosis</i> [n = 1], <i>Diarrhea</i> [n = 9], <i>Erythema</i> [n = 13], <i>Eye pruritus</i> [n = 3], <i>Eye swelling</i> [n = 5], <i>Face oedema</i> [n = 7], <i>Hypersensitivity</i> [n = 31], <i>Hypotension</i> [n = 8], <i>Hypoxia</i> [n = 1], <i>Laryngospasm</i> [n = 5], <i>Lip oedema</i> [n = 1], <i>Lip swelling</i> [n = 3], <i>Loss of consciousness</i> [n = 6], <i>Ocular hyperaemia</i> [n = 2], <i>Oxygen saturation decreased</i> [n = 4], <i>Pharyngeal oedema</i> [n = 1], <i>Pharyngeal swelling</i> [n = 3], <i>Pruritus</i> [n = 34], <i>Rash</i> [n = 36], <i>Rash erythematous</i> [n = 1], <i>Rash macular</i> [n = 1], <i>Rash pruritic</i> [n = 7], <i>Rhinorrhea</i> [n = 4], <i>Shock</i> [n = 1], <i>Stridor</i> [n = 2], <i>Swelling face</i> [n = 7], <i>Swelling of eyelid</i> [n = 4], <i>Swollen tongue</i> [n = 9], <i>Throat irritation</i> [n = 8], <i>Throat tightness</i> [n = 6], <i>Tongue oedema</i> [n = 1], <i>Type I hypersensitivity</i> [n = 1], <i>Urticaria</i> [n = 21] and <i>Vomiting</i> [n = 8]; [Total number of events = 366]. • Gender: Male = 31 and Female = 145 • Age range: 17 years to 93 years when age is reported • Serious events: n = 154 with seriousness criteria: Death = 10, Life threatening = 12, Disability/permanent damage = 5, Caused/prolonged hospitalization = 37 and Other: medically important condition = 117 • Time to onset after the first dose: 0-2 days = 173, 3-7 days = 13, 8-14 days = 15, 15-30 days = 3, ≥31 days = 10, unknown = 152 • Outcome at the time of reporting: Fatal = 10, No recovered/not resolved = 78, Recovered/resolved with sequelae = 3, Recovered/resolved = 107, Recovering/resolving = 43, Unknown = 125 • The postmarketing reporting rate is 0.14/100 000 doses distributed.
Risk factors and risk groups	Known hypersensitivity to any component of COVID-19 vaccine and/or a history of allergic reactions are considered to be risk factors for the development of anaphylaxis.
Preventability	Individuals with known hypersensitivity to any component of COVID-19 vaccine should not undergo vaccination. In individuals with no known hypersensitivity to any component of COVID-19 vaccine, prevention of anaphylaxis may not be possible; and therefore, appropriate supervision and treatment should always be available at the time of vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose.
Impact on the risk-benefit balance of the product	Anaphylactic reaction in an individual can be impactful (medically important) because it is a potentially life-threatening or fatal event requiring medical intervention. As the frequency is rare, the impact on the benefit-risk balance of the product is considered not relevant.
Public health impact	There is no public health impact currently.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PT: Preferred Term; CI: Confidence Interval; DLP: Data Lock Point; SMQ: Standardized MedDRA Query.

Table 9 - Important potential risk: Vaccine associated enhanced disease, including VAERD

Potential risk	Vaccine associated enhanced disease, including VAERD
Potential mechanism(s)	The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from non-clinical studies. Although animal models of SARS-CoV-2 infection may elucidate mechanisms of immune protection, we need observations of enhanced disease in individuals who receive COVID-19 vaccines to understand the risk of immune enhancement of disease (6). The VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD may be

Potential risk	Vaccine associated enhanced disease, including VAED
	specific to the lower respiratory tract or may be part of a systemic process. The vaccine induces a Th1-biased immune response, which is considered less likely to be associated with VAED. Less severe cases of SARS were associated with accelerated induction of a Th1 cell response; whereas, Th2 cell responses have been associated with enhancement of lung disease following infection in hosts parenterally vaccinated with inactivated SARS-CoV vaccines (7).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data. The VAED has been rarely encountered with existing vaccines or viral infections. It was observed in children given formalin-inactivated whole-virus vaccines against Respiratory Syncytial Virus and measles virus (6). No events of VAED/VAERD have been reported in the clinical development programme. 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 (8) (9).
Characterization of risk	The VAED/VAERD, if it would occur in vaccinated persons, would manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (eg, older or immunocompromised, immunocompromised children, and children with chronic conditions) having higher rates of fatal outcomes, or for observation of an unfavorable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated. Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) <i>Participants 18 years of age and older</i> No events of VAED/VAERD have been reported in adult participants in the clinical development programme and in fact the vaccine has been shown to prevent severe illness. <i>Participants 12 to < 18 years of age</i> No events of VAED/VAERD have been reported in participants 12 to < 18 years of age in the clinical development program. Postmarketing experience (Nuvaxovid (Original, Wuhan Strain)) As of 19-Dec-2025, there were seven ICSRs reported of VAED (including VAERD) according to the prescribed search strategy (PTs: <i>Antibody-dependent enhancement; Enhanced respiratory disease</i>). The cases involved six males and one female, 33 – 71 years of age). All cases were reported from South Korea. The seven cases were considered to be medically significant by convention, based on Important Medical Event criteria, however, these cases did not meet the BC level 1 – 3 criteria for VAED/VAERD. As there was insufficient case information to make a causal assessment, the company causality was considered indeterminate. The postmarketing reporting rate is 0.005/100 000 doses distributed. Postmarketing experience (Nuvaxovid XBB.1.5) Cumulatively, as of 19-Dec-2025, no initial or follow-up ICSR was retrieved of VAED (including VAERD) according to the prescribed search strategy (PTs: <i>Antibody-dependent enhancement; Enhanced respiratory disease</i>). Postmarketing experience (Nuvaxovid JN.1) Cumulatively, as of 19-Dec-2025, no initial or follow-up ICSR was retrieved of VAED (including VAERD) according to the prescribed search strategy (PTs: <i>Antibody-dependent enhancement; Enhanced respiratory disease</i>).

Potential risk	Vaccine associated enhanced disease, including VAERD
Risk factors and risk groups	There are no known risk factors or specific risk populations identified for VAED/VAERD. The demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials in clinical development of a COVID-19 vaccine (7). Population-based surveillance might give more insight into this, should any VAED occur.
Preventability	Prevention of VAED/VAERD in the context of SARS-CoV-2 is currently unknown. Population-based surveillance might give more insight in this, should any VAED occur.
Impact on the risk-benefit balance of the product	Vaccine-associated enhanced disease (including VAERD) may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED/VAERD may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation; and patients diagnosed with acute respiratory distress syndrome have poorer prognosis and potentially higher mortality rate. However, as no cases have been reported, there is no impact on the benefit-risk balance.
Public health impact	As this safety concern is currently theoretical and has not been observed in the completed/ongoing trials in relation to NVX-CoV2373/NVX-CoV2601/NVX-CoV2705 administration, there is no public health impact at this time.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; VAED: Vaccine associated enhanced disease; VAERD: vaccine-associated enhanced respiratory disease; SARS: Severe Acute Respiratory Syndrome; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; ICSR: Individual Case Study Report; BC: Brighton Collaboration; PT: Preferred Term.

Table 10 - Important potential risk: Atrial fibrillation and/or Atrial flutter

Potential risk	Atrial fibrillation and/or Atrial flutter
Potential mechanism(s)	The possible underlying mechanisms remain unclear. Aberrant inflammatory responses and activation or dysregulation of the immune system could be involved in the biological plausibility of atrial fibrillation and/or atrial flutter induced by COVID-19 immunization (10).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data.
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) No serious cases of atrial fibrillation and/or atrial flutter were reported from clinical sponsored studies. Postmarketing experience (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) - Cumulatively, 29 cases were retrieved (search strategy: <i>Atrial fibrillation and Atrial flutter</i> [PTs]) till DLP 19-Dec-2025. - The reported PTs were <i>Atrial fibrillation</i> [n = 24] and <i>Atrial flutter</i> [n = 7] [Total number of events = 31]. - Gender: Male = 19 and Female = 10 - Age range: 22 years to 81 years when age is reported - Serious events: n = 28 with seriousness criteria: Life threatening = 2, Caused/prolonged hospitalization = 13 and Other: medically important condition = 27

Potential risk	Atrial fibrillation and/or Atrial flutter
	- Time to onset: 0-1 days = 4, 2-7 days = 4, 8-14 days = 1, 15-30 days = 2, ≥31 days = 4, unknown = 16 - Outcome at the time of reporting: No recovered/not resolved = 6, Recovered/resolved = 7, Recovering/resolving = 6, Unknown = 12 - A total of six cases were retrieved involving patients under 50 years of age, wherein two patients experienced atrial fibrillation within 14 days of vaccination. Out of these two cases, one case has a history of atrial fibrillation. Three cases did not report latency and/or were lacking details of medical history and one case had a latency of 329 days. - The postmarketing reporting rate is 0.02/100 000 doses distributed.
Risk factors and risk groups	There are no specific risk factors for atrial fibrillation and/or atrial flutter however, based on mechanistic plausibility and extrapolation from broader post-vaccination arrhythmia literature, individuals with the following groups would be considered at theoretical increased risk: - Individuals with prior atrial fibrillation and/or atrial flutter - Pre-existing atrial cardiomyopathy (structural or electrophysiologic) - Advanced age - Heightened inflammatory or autoimmune activity - Prior myocardial inflammatory conditions (eg, myocarditis) - Susceptibility to autonomic imbalance
Preventability	Prevention of atrial fibrillation and/or atrial flutter in the context of COVID-19 vaccination is currently unknown. Population-based surveillance might give more insight.
Impact on the risk-benefit balance of the product	There is no impact on the benefit-risk balance of the product.
Public health impact	There is no public health impact currently.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PT: Preferred Term; DLP: Data Lock Point.

Table 11 - Important potential risk: Cerebrovascular accident

Potential risk	Cerebrovascular accident
Potential mechanism(s)	The underlying mechanisms linking vaccination to stroke are not fully elucidated but may involve vaccine-induced immune thrombotic thrombocytopenia, molecular mimicry, and platelet activation pathways (11).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data.
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) Two serious cases of cerebrovascular accident were reported from clinical sponsored studies. Both the cases were considered as not related to study vaccine.

Potential risk	Cerebrovascular accident Postmarketing experience (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) - Cumulatively, 24 cases were retrieved (Search strategy: <i>Hemorrhagic central nervous system vascular conditions</i> (SMQ) (SMQ Narrow), <i>Ischaemic central nervous system vascular conditions</i> (SMQ) (SMQ Narrow)) till DLP 19-Dec-2025. - The reported PTs were <i>Cerebrovascular accident</i> [n = 15], <i>Transient ischemic attack</i> [n = 4], <i>Ischemic stroke</i> [n = 2], <i>Thalamic infarction</i> [n = 1], <i>Cerebral infarction</i> [n = 1], <i>Brain stem infarction</i> [n = 1] and <i>Carotid artery disease</i> [n = 1]; [Total number of events = 25]. - Gender: Male = 12, Female = 11 and Unknown = 1 - Age range: 20 years to 96 years when age is reported; seven cases were reported <50 years of age. - Serious events: n = 25 with seriousness criteria: Death = 2, Life threatening = 2, Caused/prolonged hospitalization = 17, Disability/permanent damage = 3 and Other: medically important condition = 25 - Time to onset: 0-1 days = 2, 2-7 days = 8, 8-28 days = 3, ≥29 days = 7, unknown = 5 - Outcome at the time of reporting: Fatal = 2, No recovered/not resolved = 6, Recovered/resolved = 2, Recovered with sequelae = 2, Recovering/resolving = 5, Unknown = 8 - A total of seven cases were retrieved involving patients under 50 years of age, wherein three patients, with no reported medical history, experienced transient ischemic attack/Brainstem infarction/Thalamic infarction within 14 days of vaccination. Remaining four cases reported cerebrovascular accident, wherein latency was two months, 65 days, 68 days and latency unknown, respectively. - Causal role of company vaccine for one case can be excluded since patient was incidentally found to have atherosclerotic changes in vascular imaging which are significant risk factors for the causation of the event. - For the remaining cases, a causal role of company vaccine cannot be established since the cases lacked information regarding any baseline/event-associated investigations, any pre-existing conditions, concomitant medications (whether on any antiplatelets or anticoagulants, any details about cerebrovascular risks, hydration status and electrolyte imbalances, which could have occurred over time. Not enough information to determine causality. - The postmarketing reporting rate is 0.018/100 000 doses distributed.
Risk factors and risk groups	There are no specific risk factors for cerebrovascular accident however, the following groups would be considered at theoretical increased risk: - Baseline prothrombotic conditions - Estrogen-related thrombotic risk - Cerebrovascular or cardiovascular comorbidities - Advanced age - Systemic inflammatory hyperreactivity
Preventability	Prevention of cerebrovascular accident in the context of COVID-19 vaccination is currently unknown. Population-based surveillance might give more insight.
Impact on the risk-benefit balance of the product	There is no impact on the benefit-risk balance of the product.
Public health impact	There is no public health impact currently.

Potential risk Cerebrovascular accident

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PT: Preferred Term; DLP: Data Lock Point; SMQ: Standardized MedDRA Query.

Table 12 - Important potential risk: Cranial Nerve VIII Disorders (including Vestibular Neuronitis)

Potential risk	Cranial Nerve VIII Disorders (including Vestibular Neuronitis)
Potential mechanism(s)	The underlying mechanisms linking COVID-19 vaccination to vestibular neuronitis remain unclear. It is possible that the activation of the immune system triggered by the vaccine may lead to an inflammatory response that affects the vestibular nerve. Another hypothesis suggests that viral reactivation, particularly Herpes simplex virus or Varicella Zoster virus, may contribute to the development of vestibular neuronitis following vaccination (12).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data.
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) No serious cases of cranial nerve VIII disorders (including vestibular neuronitis) were reported from clinical sponsored studies. Postmarketing experience (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) Cumulatively, no cases of cranial nerve VIII disorders (including vestibular neuronitis) were reported during the post-marketing experience (Search strategy: <i>VIIIth cranial nerve disorders</i> [HLT]) till DLP 19-Dec-2025.
Risk factors and risk groups	The following groups may be theoretically at higher risk: • Individuals with autoimmune predisposition or prior autoimmune neurologic disease • Those with pre-existing vestibular or peripheral neuropathies • Individuals with high inflammatory reactivity • Patients with latent neurotropic viral susceptibility • Those with central nervous system demyelinating conditions • Individuals prone to cytokine-driven vestibular dysfunction
Preventability	Prevention of cranial nerve VIII disorders (including vestibular neuronitis) in the context of COVID-19 vaccination is currently unknown. Population-based surveillance might give more insight.
Impact on the risk-benefit balance of the product	There is no impact on the benefit-risk balance of the product.
Public health impact	There is no public health impact currently.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; HLT: High Level Term; DLP: Data Lock Point.

Table 13 - Important potential risk: Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)

Potential risk	Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI)
Potential mechanism(s)	Though the exact pathophysiology to explain the association between cranial nerve palsies and COVID-19 vaccination remains unknown, multiple hypothetical mechanisms exist. Since cranial nerve palsies have been reported both after COVID-19 infection and vaccination, an immune-mediated mechanism seems the most plausible. Alternatively, demyelination or localized vasculitis due to immune processes could damage the cranial nerves in their central or peripheral pathways (13).
Evidence source(s) and strength of evidence	Literature on viral vaccines, safety information of other SARS-CoV-2 vaccines, clinical trials, and post-market safety data.
Characterization of risk	Clinical trial experience (NVX-CoV2373, NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), NVX-CoV2705 (JN.1)) No serious cases of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) were reported from clinical sponsored studies. Postmarketing experience (Nuvaxovid, Nuvaxovid XBB.1.5 and Nuvaxovid JN.1) - One case was retrieved cumulatively (Search strategy: <i>Eye movement disorders</i> [HLT]) till DLP 19-Dec-2025. This case involved a 72-year-old female who experienced IIIrd nerve paralysis (PT: <i>IIIrd nerve paralysis</i>, Seriousness criteria: Hospitalization and Medically Significant) one day after vaccination with Nuvaxovid XBB.1.5. Co-reported PTs included <i>Vision blurred</i> and <i>Eyelid function disorder</i>. At the time of reporting, the outcome of the event was not recovered/not resolved. Follow up information has been requested but not available at this time. - The postmarketing reporting rate is 0.0007/100 000 doses distributed.
Risk factors and risk groups	There are no specific risk factors for ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) however, theoretical risk may be higher in individuals who have: - Autoimmune disease or prior autoimmune neurologic events - Pre-existing neuropathy or neurologic instability - High inflammatory reactivity - Central nervous system demyelinating diseases - Microvascular vulnerability
Preventability	Prevention of ocular motor cranial nerve disorders (ie, cranial nerve disorders affecting cranial nerves III, IV, or VI) in the context of COVID-19 vaccination is currently unknown. Population-based surveillance might give more insight.
Impact on the risk-benefit balance of the product	There is no impact on the benefit-risk balance of the product.
Public health impact	There is no public health impact currently.

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PT: Preferred Term; DLP: Data Lock Point; HLT: High Level Term.

16.4.2 Missing information

Table 14 - Missing information: Use in pregnancy and while breastfeeding

Missing Information	Use in pregnancy and while breastfeeding
Evidence source(s) and strength of evidence	There is limited experience with use of Nuvaxovid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development. Administration of Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus. It is unknown whether Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 is excreted in human milk. No effects on the breast-fed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Nuvaxovid/Nuvaxovid XBB.1.5/Nuvaxovid JN.1 is negligible.
Population in need for further characterization	Pregnant and breastfeeding women.
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, vaccination of pregnant and/or breastfeeding women will occur.

Table 15 - Missing information: Use in immunocompromised patients

Missing Information	Use in immunocompromised patients
Evidence source(s) and strength of evidence	The vaccine has not been studied in individuals with immunocompromised conditions, except for subjects with HIV. Subjects with HIV were not excluded from the clinical programme, and 244 participants were enrolled in the 2019nCoV-501 study. The safety profile of NVX-CoV2373 in HIV-positive participants in this study was similar to that seen in HIV-negative participants. There is no evidence that the safety profile of this population receiving NVX-CoV2373/NVX-CoV2601 will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Population in need for further characterization	Individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants.
Anticipated risk/consequence of the missing information	Vaccines may be less effective in severely immunocompromised patients, as the vaccinees weakened immune system may not mount a sufficient response.

HIV: Human Immunodeficiency Virus.

Table 16 - Missing information: Use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)

Missing Information	Use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)
Evidence source(s) and strength of evidence	The vaccine has not been studied in frail (unstable) individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail

Missing Information	Use in frail patients with comorbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)
	patients with comorbidities (eg, COPD, DM, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19. There is no evidence that the safety profile of this population receiving NVX-CoV2373/NVX-CoV2601 will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Population in need for further characterization	Frail individuals with comorbidities (eg, COPD, DM, chronic neurological disease, cardiovascular disorders).
Anticipated risk/consequence of the missing information	Frail individuals with unstable and/or severe health conditions and comorbidities may experience a different outcome of the vaccination than that achieved in generally healthy individuals administered vaccines.

COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; COVID-19: Coronavirus disease 2019;

Table 17 - Missing information: Use in patients with autoimmune or inflammatory disorders

Missing Information	Use in patients with autoimmune or inflammatory disorders
Evidence source(s) and strength of evidence	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. There is no evidence from clinical studies to date that the safety profile of this population differs with that of the general population. However, given the paucity of data, the possibility cannot be excluded.
Population in need for further characterization	Patients with autoimmune or inflammatory disorders.
Anticipated risk/consequence of the missing information	Individuals with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines.

Table 18 - Missing information: Interaction with other vaccines

Missing Information	Interaction with other vaccines
Evidence source(s) and strength of evidence	There is limited information on the safety of the vaccine when administered with other vaccines within 28 days prior to the first dose or any dose of NVX-CoV2373, except for seasonal influenza vaccine, <14 days. Approximately 400 participants were concurrently administered an inactivated seasonal influenza vaccine with NVX-CoV2373 or placebo. The binding antibody response to SARS-CoV-2 was lower when NVX-CoV2373 was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown. Concomitant administration of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 with other vaccines has not been studied.
Population in need for further characterization	Individuals who will receive other vaccines within 28 days prior to or 14 days after immunization with Nuvaxovid, Nuvaxovid XBB.1.5, and Nuvaxovid JN.1.
Anticipated risk/consequence of the missing information	Theoretically, vaccines may interact with each other and change the immune response to either vaccine or induce safety concerns.

Table 19 - Missing information: Long-term Safety

Missing Information	Long-term Safety
Evidence source(s) and strength of evidence	Understanding of the long-term safety profile of NVX-CoV2373/NVX-CoV2601/NVX-CoV2705 is currently limited. Follow-up in clinical trials is planned to range from 6-24 months following vaccinations. The maximum follow-up in clinical studies post dose two will be 24 months.
Population in need for further characterization	Individuals receiving Nuvaxovid, Nuvaxovid XBB.1.5, and Nuvaxovid JN.1.
Anticipated risk/consequence of the missing information	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. Whilst there is currently no evidence to suspect an adverse long-term safety profile, given the paucity of data, the possibility cannot be excluded.

VAED: Vaccine associated enhanced disease; VAERD: vaccine-associated enhanced respiratory disease.

16.5 EFFECTIVENESS OF RISK MINIMIZATION

No effectiveness evaluation is established for COVID-19 vaccine since there are no RMMs beyond routine.

The currently approved risk management activities including the communication of the risk in the product labelling and its legal status are sufficient to manage the risks of this product.

17 BENEFIT EVALUATION

17.1 IMPORTANT BASELINE EFFICACY AND EFFECTIVENESS INFORMATION

The approved indications for COVID-19 vaccine are presented in Section 2.

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

Baseline effectiveness of Nuvaxovid XBB.1.5 and Nuvaxovid JN.1 for individuals 12 years of age and older was inferred from studies which evaluated the primary series and booster vaccination with COVID-19 vaccine Original, Wuhan strain and was supported by a study of a booster dose of an investigational vaccine targeting the Omicron BA.5 variant of SARS-CoV-2 in individuals 18 years of age and older, and by a study of a booster dose of an investigational vaccine targeting the Omicron BA.1 and BA.5 variants of SARS-CoV-2 in individuals 18 to 64 years of age.

17.1.1 Adolescents 12 to <18 years of age

17.1.1.1 Primary Series (Original, Wuhan strain)

Study 2019nCoV-301

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

17.1.1.1.1 Efficacy in Adolescents 12 to <18 years of age

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

A total of 1799 participants assigned in a 2:1 ratio to receive two doses of COVID-19 vaccine (n = 1205) or placebo (n = 594) by intramuscular injection 21 days apart represented the primary efficacy population.

The COVID-19 was defined as first episode of polymerase chain reaction (PCR)-confirmed mild, moderate, or severe COVID-19 with at least one or more of the predefined symptoms within each severity category. There were 20 cases of PCR-confirmed symptomatic mild COVID-19 (COVID-19 vaccine, n = 6; placebo, n = 14) resulting in a point estimate of efficacy of 79.5% (95% CI: 46.8%, 92.1%).

At the time of this analysis, the Delta (B.1.617.2 and AY lineages) variant of concern (VOC) was the predominant variant circulating in the US and accounted for all cases where sequence data are available (11/20, 55%).

17.1.1.1.2 Immunogenicity in Adolescents 12 to <18 years of age

An analysis of the SARS-CoV-2 nAb response 35 days after Dose two was conducted in adolescent participants seronegative to anti-SARS-CoV-2 nucleoprotein/PCR-negative at baseline compared with that observed in seronegative/PCR-negative adult participants aged 18 to less than 26 years from the adult main study (Per Protocol Immunogenicity [PP-IMM] Population, before crossover). Noninferiority (lower bound 95% CI for the geometric mean ratio [GMR] > 0.67 [1.25], point estimate of the ratio of Geometric Mean Titres [GMTs] ≥ 0.82; and the lower bound of the two-sided 95% CI for difference of seroconversion rates [SCRs] [SCR 12 through 17 years minus SCR 18 through 25 years] > -10%) was met.

17.1.1.2 Booster dose (Original, Wuhan strain)

17.1.1.2.1 Immunogenicity in Adolescents 12 to <18 years of age

The safety and immunogenicity of a booster dose of COVID-19 vaccine was evaluated in a Phase 3, multinational, multicentre, randomized, observer-blinded, placebo-controlled Paediatric Expansion study involving 220 adolescents 12 through 17 years of age conducted in the US. Of these, 110 participants received a booster dose after first receiving placebo during the initial (pre-crossover) vaccination period followed by active vaccination during the blinded crossover period (Cohort 1) and 110 who received a booster dose after first receiving active vaccination during the initial (pre-crossover) vaccination period followed by placebo during the blinded crossover period (Cohort 2) from 58 sites in the US. All adolescent participants aged 12 through 17 years of age were seronegative to SARS-CoV-2 at baseline.

The study assessed the immune response (nAb against SARS-CoV-2 wild-type virus, serum immunoglobulin G [IgG] antibody to SARS-CoV-2 spike protein immediately prior to and at 28 days after administration of a booster dose of COVID-19 vaccine and evaluated the overall safety profile of COVID-19 vaccine through 28 days after the booster dose in 220 randomly selected adolescent participants aged 12 through 17 years of age.

A total of 2122 participants received two doses of COVID-19 vaccine (0.5 mL, 5 micrograms three weeks apart) as the primary vaccination series. A total of 1499 participants received a booster dose of COVID-19 vaccine approximately nine months after completing the primary vaccination series, and of those 220 were selected for immunogenicity analysis. This resulted in 53 participants eligible to be analysed as part of the primary endpoint.

A single booster dose of COVID-19 vaccine induced an approximate 34.2-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose with a serum IgG geometric mean ELISA unit (GMEU) of 388 263.3 ELISA Unit/mL compared to a GMEU of 11 339.4 ELISA Unit/mL pre-booster and an approximate 2.5-fold increase from peak GMEU (156 286.4 ELISA Unit /mL), 14 days following Dose two of the primary series.

An approximate 27.7-fold increase in nAbs was shown from a GMT of 426.7 pre-booster to a GMT of 11 824.4 post-booster and an approximate 2.7-fold increase from a peak GMT (14 days post-Dose two) of 4434.0.

A single booster dose of COVID-19 vaccine administered to adolescent participants 12 through 17 years of age elicited robust immune responses (nAb [Microneutralization Assay of the Dilution to Achieve 50% Neutralization {MN₅₀}], serum IgG antibody, and human Angiotensin Converting Enzyme 2 receptor binding inhibition) against the SARS-CoV-2 wild-type virus (ancestral Wuhan strain) at 28 days after the booster dose of COVID-19 vaccine and were higher than those reported at 14 days after the second dose of COVID-19 vaccine of the primary vaccination series. Based on nAb responses, non-inferiority was achieved for Geometric Mean Fold Rises and for the differences

in SCRs using the baseline of the first dose of COVID-19 vaccine in the pre-crossover period (Cohort 2). Higher immune responses for pseudovirus-based nAb against the Omicron BA.4/5 variant and serum IgG antibody against the Omicron BA.1 variant were also seen after the single booster dose of COVID-19 vaccine.

17.1.2 Adults 18 years of age and older

17.1.2.1 Primary Series - Original, Wuhan strain

17.1.2.1.1 Efficacy in Adults 18 years of age and older

Study 2019nCoV-301 - Original, Wuhan strain

Upon enrolment in the adult main study, participants were stratified by age (18 to 64 years and ≥ 65 years) and assigned in a 2:1 ratio to receive COVID-19 vaccine or placebo.

The primary efficacy analysis population (referred to as the per protocol-efficacy [PP-EFF] analysis set) included 25 452 participants who received either COVID-19 vaccine ($n = 17\,312$) or placebo ($n = 8\,140$), received two doses (Dose one on day 0; Dose two at day 21), did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through seven days after the second dose. Demographic and baseline characteristics were balanced amongst participants who received COVID-19 vaccine and those who received placebo.

Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates for male and female participants and racial groups, and across participants with medical comorbidities associated with high risk of severe COVID-19. There were no meaningful differences in overall vaccine efficacy in participants who were at increased risk of severe COVID-19 including those with one or more comorbidities that increase the risk of severe COVID-19 (eg, body mass index ≥ 30 kg/m², chronic lung disease, DM type 2, cardiovascular disease, and chronic kidney disease).

Efficacy results reflect enrolment that occurred during the time period when strains classified as VOC or Variants of Interest (VOI) were predominantly circulating in the two countries (US and Mexico) where the study was conducted.

Vaccine efficacy of COVID-19 vaccine to prevent the onset of COVID-19 from seven days after Dose two was 90.4% (95% CI 82.9 – 94.6). No cases of severe COVID-19 were reported in the 17 312 COVID-19 vaccine participants compared with four cases of severe COVID-19 reported in the 8140 placebo recipients in the PP-EFF analysis set.

Study 2019nCoV-302 - Original, Wuhan strain

Study 2019nCoV-302 was a Phase 3, multicentre, randomized, observer-blinded, placebo-controlled study in participants 18 to 84 years of age in the UK. Upon enrolment, participants were stratified by age (18 to 64 years; 65 to 84 years) to receive COVID-19 vaccine or placebo.

The PP-EFF analysis set included 14 039 participants who received either COVID-19 vaccine (n = 7020) or placebo (n = 7019), received two doses (Dose one on day 0; Dose two at median 21 days) did not experience an exclusionary protocol deviation, and did not have evidence of SARS-CoV-2 infection through seven days after the second dose.

Demographic and baseline characteristics were balanced amongst participants who received COVID-19 vaccine and participants who received placebo.

Vaccine efficacy of COVID-19 vaccine to prevent the onset of COVID-19 from seven days after Dose two was 89.7% (95% CI 80.2 – 94.6). No cases of severe COVID-19 were reported in the 7020 COVID-19 vaccine participants compared with four cases of severe COVID-19 reported in the 7019 placebo recipients in the PP-EFF analysis set.

These results reflect enrolment that occurred during the time period when the B.1.17 (Alpha) variant was circulating in the UK. Identification of the Alpha variant was based on S gene target failure by PCR.

17.1.2.2 Booster Dose - Original, Wuhan strain and Omicron BA.1 and BA.5 variants

17.1.2.2.1 Immunogenicity in Adults 18 years of age and older

Study 2019nCoV-101 Part 2 - Original, Wuhan strain

The safety and immunogenicity of a booster dose of COVID-19 vaccine was evaluated in the completed Phase 2 randomized, observer-blinded, placebo-controlled clinical study administered as a single booster dose (Study 2019nCoV-101, Part 2) in healthy adult participants aged 18 to 84 years of age who were seronegative to SARS-CoV-2 at baseline.

A total of 255 participants received two doses of COVID-19 vaccine (0.5 mL, 5 micrograms three weeks apart) as the primary vaccination series. A subset of 105 participants received a booster dose of COVID-19 vaccine approximately six months after receiving Dose two of the primary series.

A single booster dose of COVID-19 vaccine induced a 31.2-fold increase in the immune response against the Wuhan (ancestral) strain 28 days after receipt of the dose (Day 217) with serum IgG GMT of 200 243 ELISA Units compared to a GMT of 6151 ELISA Units pre-booster (Day 189). A GMR of 4.7 from peak GMT (42 173 ELISA Units), 14 days following Dose two of the primary series was demonstrated.

A 79.6-fold increase in nAbs was shown from a GMT of 68 pre-booster (Day 189) to a GMT of 5542 post-booster (Day 217). A GMR of 4.0 from a peak GMT (14 days post-Dose two) of 15 461 was demonstrated.

Study 2019nCoV-501 - Original, Wuhan strain

In Study 2019nCoV-501, a Phase 2a/b randomized, observer-blinded, placebo-controlled study, the safety and immunogenicity of booster dose was evaluated in healthy HIV-negative adult participants 18 to 84 years of age and medically stable People living with human immunodeficiency virus (PLHIV) 18 to 64 years of age who were seronegative to SARS-CoV-2 at baseline. The PLHIV were medically stable (free of opportunistic infections), receiving highly active and stable antiretroviral therapy, and having an HIV-1 viral load of <1000 copies/mL.

A total of 1804 participants PP-IMM analysis set received a booster dose of COVID-19 vaccine approximately six months after completion of the primary series of COVID-19 vaccine (Day 201).

A 17.1-fold increase was shown in serum IgG GMT assessed at Day 236 (114 679 ELISA Unit) from the pre-boost GMT at Day 201 (5950 ELISA Unit). A GMR of 2.2 was demonstrated from peak GMT (52 023 ELISA Unit) at Day 35 following completion of the primary series.

A 20.6-fold increase in nAbs was shown from a GMT of 146 pre-booster (Day 201) to a GMT of 3726 post-booster (Day 236). A GMR of 2.7 was demonstrated from a peak GMT (14 days post-Dose two) of 1352.

Study 2019nCoV-301 Original, Wuhan Strain

In the open-label booster phase of Study 2019nCoV-301, participants 18 years of age and older received a single booster dose of the COVID-19 vaccine at least six months after completion of the primary series. A subset of 226 participants were included in the PP-IMM analysis set as they did not have serologic or virologic evidence of SARS-CoV-2 infection up to 28 days post booster dose.

Prespecified immunogenicity non-inferiority analyses included an assessment of MN₅₀ GMT ratio and difference in SCRs. Seroconversion for a participant was defined as achieving a 4-fold rise in MN₅₀ from baseline (before the booster dose and before the first dose of the primary series).

The analysis of the GMT ratio of MN₅₀ following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > 0.67) and point estimate > 0.83.

The analysis of the difference in SCRs following the booster dose compared to the primary series met the non-inferiority criteria for a booster response (lower limit of the 95% CI > -10%).

In addition, a single booster dose of the COVID-19 Vaccine elicited a robust immune response (serum IgG antibody) against the Omicron BA.1 variant at 28 days after booster vaccination that were higher than that reported at 14 days after primary series vaccination in the same participants.

Additionally, in Study 301, approximately six months after completion of the third dose (first booster) with COVID-19 vaccine, 356 participants at selected sites received a fourth dose (second booster) of COVID-19 vaccine. Dosing was initiated on 19 September 2022, with enrolment completed on 01 October 2022. Immunogenicity data were collected from 331 participants immediately prior to administering the fourth dose and at 28 days after vaccination based on data cut-off date of 08 November 2022. Safety data were assessed in 356 participants from the time of administration of the second booster dose through the data cut-off date of 08 November 2022.

Study 2019nCoV-311 Parts 1 and 2, Original, Wuhan strain and Omicron BA.1 or BA.5 variant

Study 2019nCoV-311 is a completed 2-part, Phase 3, randomized, observer-blinded study conducted in Australia to evaluate the safety and immunogenicity in adults of a booster dose of COVID-19 vaccine in adults in Australia.

In Part 1, a subgroup of participants 18 to 64 years of age who previously received three doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or monovalent vaccine (Omicron BA.1). The booster doses were administered at a median of 182 and 177 days after the last vaccination, respectively. Neutralizing antibody titres for the Omicron BA.1 virus, measured by a MN₅₀, were evaluated at 14 days after vaccination. Participants included in the day 14 per protocol analysis set population (n = 240) had no serologic or virologic evidence of SARS-CoV-2 infection prior to the booster dose.

Pre-specified immunogenicity analyses included an assessment of MN₅₀ GMT ratio and difference in seroresponse rates (SRRs). Seroresponse rate was defined as the percentage of participants achieving a 4-fold rise in MN₅₀ from baseline (before the first dose of the study vaccine).

The analysis of the GMT ratio following the booster dose with monovalent vaccine (Omicron BA.1) compared to the booster dose with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) met the superiority criterion for success (lower limit of the 95% CI > 1.0).

The lower limit of the two-sided 95% CI for the difference in SRRs (percentage) was 10.3%, which met the non-inferiority criterion for success (lower limit of 95% CI for the percentage difference of > -5%).

In sensitivity analyses using a per protocol analysis set that did not exclude participants with serologic evidence of SARS-CoV-2 infection (per protocol 2 Analysis Subset, n = 491), nAb responses against the Omicron BA.1 virus induced by the monovalent vaccine (Omicron BA.1) were compared with nAb responses against the Omicron BA.1 virus induced by the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) 14 days after study vaccination.

The GMTs were 318.2 (95% CI: 269.8, 375.3) in the monovalent vaccine (Omicron BA.1) group (n = 247) and 218.1 (95% CI: 186.0, 255.7) in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group (n = 244), resulting in an estimated GMT ratio of the monovalent vaccine (Omicron BA.1) versus the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) of 1.5 (95% CI: 1.36, 1.77).

The SRRs (percentage) were 54.3% in the monovalent vaccine (Omicron BA.1) group and 32.0% in the Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) group, resulting in a difference in SRRs (percentage) of 22.3% (95% CIs: 13.6%, 30.6%).

In Part 2, a subgroup of participants 18 years of age and older who previously received at least 3 doses of the Pfizer-BioNTech COVID-19 Vaccine or the Moderna COVID-19 Vaccine, received one of the following as a booster dose: Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) or monovalent vaccine (Omicron BA.5). The booster doses were administered a median of 389 and 328 days after the last vaccination, respectively. Neutralizing antibody titers against a pseudovirus expressing the SARS-CoV-2 spike protein from the Omicron BA.5 virus, measured by pseudovirus neutralization assay (Inhibitory Dilution at a Concentration of 50% [ID₅₀]), were evaluated at 28 days after vaccination. Participants included in the day 28 per protocol analysis set population (n = 462) had no virologic evidence of SARS-CoV-2 infection at time of the booster dose.

Exploratory immunogenicity analyses included an assessment of the ID₅₀ GMT ratio and difference in SRRs. Seroresponse rate was defined as the percentage of participants achieving a 4-fold rise in ID₅₀ from baseline (before the first dose of the study vaccine).

The GMT ratio following the booster dose with monovalent vaccine (Omicron BA.5) compared with the booster dose with Novavax COVID-19 Vaccine, Adjuvanted (Original monovalent) was 2.5 (two-sided 95% CI: 2.10, 2.94).

The difference in SRR (percentage) between the booster dose with monovalent vaccine (Omicron BA.5) and the booster dose with Novavax Vaccine, Adjuvanted (Original monovalent) was 33.2% (two-sided 95% CI: 25.4%, 40.7%).

17.1.3 Elderly Population

The efficacy of COVID-19 vaccine was consistent between elderly (≥65 years) and younger individuals (18 to 64 years) for the primary series.

Participants ≥65 years of age were evaluated for efficacy in the two pivotal Phase 3 clinical trials.

In the placebo-controlled Phase 3 Study 2019nCoV-301 conducted in the US and Mexico, 11.8% (n = 2048) of enrolled participants that received the primary series were ≥ 65 years.

In the placebo-controlled Phase 3 Study 2019nCoV-302 conducted in the UK, 27.8% (n = 1953) of enrolled participants who received the primary series were ≥ 65 years.

17.2 NEWLY IDENTIFIED INFORMATION ON EFFICACY AND EFFECTIVENESS

No new relevant efficacy and/or effectiveness findings in approved indications were identified during the reporting interval.

A review of literature was performed for publications available during the period aligned with this PBRER's reporting time frame, 20 December 2024 to 19 December 2025, to identify relevant published controlled clinical trials, meta-analyses and systematic reviews on Nuvaxovid.

Seven relevant publications were identified and are described hereafter:

Vergori A, Matusali G, Lepri AC, Cimini E, Colavita F, Mariotti D, et al. Supporting equitable booster strategies: one-year real-world immunogenicity data in people with HIV (PWH) receiving different variant-adapted COVID-19 vaccines. Int J Infect Dis. 2025 Nov 7;163:108189. (14)

The study was performed to compare the 12-month immunogenicity of Nuvaxovid XBB.1.5 (protein-based) and Pfizer-BioNTech monovalent mRNA XBB.1.5 boosters in people with human immunodeficiency virus (PWH) on stable antiretroviral therapy, assessing humoral and cellular immune responses against ancestral and emerging SARS-CoV-2 variants.

Fifty (50) participants with a median age of 58 years (interquartile range, 52, 66), all previously primed with at least four monovalent mRNA doses, received either Nuvaxovid (n = 24) or mRNA vaccine (n = 26), depending on availability. Anti-receptor binding domain (RBD) IgG, nAbs against D614G, XBB.1.16, JN.1, LP.8.1, and IFN- γ T-cell activity were measured at baseline (T0), one month (T1), and 12 months (T2) post-booster.

The results demonstrated that at T1, RBD IgG titers were higher in the mRNA group than in the Nuvaxovid group (6942 versus 4143 Binding Antibody Units/mL; $p = 0.01$), but nAbs and T-cell responses showed no significant differences. At T2, humoral responses were comparable, with a trend toward higher LP.8.1 nAb titers in Nuvaxovid recipients ($p = 0.06$). Mixed-model analyses confirmed stronger short-term LP.8.1 nAb responses with mRNA, but slower waning with Nuvaxovid. No consistent differences were observed for other variants.

It was concluded that overall, mRNA boosters provided a stronger early humoral response, while Nuvaxovid may promote more sustained T-cell immunity. Both maintained robust responses over 12 months, supporting their use in PWH. Given its thermostability and accessibility, Nuvaxovid is a practical alternative when mRNA vaccines are unavailable or contraindicated.

Chappell KJ, Mordant FL, Amarilla AA, Modhiran N, Liang B, Li Z, et al. Safety and immunogenicity of a severe acute respiratory syndrome coronavirus 2 spike subunit vaccine stabilized in the prefusion conformation by a second generation molecular clamp and evaluated in adults aged 18–55 years: a randomized, double-blind, active comparator, phase I trial. J Infect Dis. 2025 Nov 25;jiaf568. (15)

A COVID-19 subunit vaccine developed with the molecular clamp (MC) platform was among the first to enter clinical trials in 2020. While the vaccine was well suited to large-scale manufacture and demonstrated a favorable safety and immunogenicity profile, it did not progress into further clinical testing due to the HIV-1–derived sequence in the MC, interfering with certain point-of-care HIV-1 diagnostic tests. A second-generation MC2 has since been developed. Here, we describe a phase I clinical trial of an MC2-stabilized SARS-CoV-2 spike subunit vaccine, UQSC2.

A phase I, double-blind, active comparator-controlled trial was conducted in Australia (ClinicalTrials.gov NCT05775887). Healthy adults (aged 18–50 years), who had previously received ≥ 3 doses of an approved mRNA SARS-CoV-2 vaccine, received a single booster dose of either UQSC2 or the approved comparator NVX-CoV2373 (Nuvaxovid; Novavax) (n = 70; 35 per group). Safety, humoral immunogenicity (including against virus variants), and cellular immunogenicity were assessed through day 183. Cases of confirmed COVID-19 infection during the study were also examined.

Both vaccines were equally well tolerated and elicited comparable increases in neutralizing humoral responses against the vaccine-matched prototypic, Wuhan strain of SARS-CoV-2.

It was concluded that UQSC2 was as well tolerated as the authorized comparator vaccine and produced an equally robust boost in neutralizing immune response. These findings support the effectiveness of the MC2 platform in producing vaccines against newly emerging variants of SARS-CoV-2 and other respiratory viruses, as well as the platform's potential use in emergency response to novel viruses.

Kuriyama K, Murakami K, Sugiura K, Sakui S, Schuring RP, Mori M. One-year follow-up of the immunogenicity and safety of a first and second booster dose of the NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults who had previously received a primary series of COVID-19 mRNA vaccine: Final report of a phase 3 open-label trial. Vaccine. 2025 Aug 30;62:127562. (16)

In this phase 3, single-arm, open-label trial in Japanese adults who had previously received a COVID-19 mRNA primary vaccination, two NVX-CoV2373 boosters, administered five months apart in the main and extension parts of the study, respectively, induced robust immune responses up to day 15 after each dose. This final report presents immunogenicity and safety findings at one year follow-up.

Immunogenicity of the first NVX-CoV2373 booster (main part) and second NVX-CoV2373 booster (extension part) was assessed at D29, D91, D181, and D366 in each study part.

Of 150 participants who received a first NVX-CoV2373 booster on D1, 21 did not participate in the extension part and 17 completed the main part. In total, 129 participants received a second booster on extension day (ED) 1, and 121 completed the extension part. In the main and extension parts, anti-SARS-CoV-2 serum IgG responses to the boosters peaked on D29 and ED15, respectively; serum nAb responses to the boosters peaked on D15 and ED29, respectively. Serum IgG and nAb titres remained relatively high in both study parts throughout the one-year follow-up compared with their pre-booster titres on D1 and ED1. There were no deaths or AEs leading to study discontinuation at one-year follow-up for both study parts. A SARS-CoV-2 infection was reported in 14.0 % (21/150) of participants in the main part and 10.9 % (14/129) in the extension part; all cases were mild/moderate in severity.

The two NVX-CoV2373 boosters induced durable anti-SARS-CoV-2 immune responses up to one year after each dose and are therefore expected to persistently protect against SARS-CoV-2 infections and severe disease outcomes in Japanese adults. No new safety concerns were identified, demonstrating the expected acceptable safety profile in healthy Japanese participants.

Alves K, Kouassi A, Plested JS, Kalkeri R, Smith K, Kaba M, et al. Immunogenicity and safety of a monovalent Omicron XBB.1.5 SARS-CoV-2 recombinant spike protein vaccine in previously unvaccinated, SARS-CoV-2 seropositive participants: Primary day-28 analysis of a phase 2/3 open-label study. Vaccine. 2025 May 10;55:127046. (17)

This was a phase 2/3, open-label, single-arm study (2019nCoV-313/ [group 2]), in which the vaccine-naïve participants ≥ 18 years with previous SARS-CoV-2 infection received one dose of NVX-CoV2601. The analysis compared the 28-day immunogenicity and safety of NVX-CoV2601 in vaccine-naïve and previously vaccinated (≥ 3 prior mRNA-based vaccines, from 2019nCoV-313 group 1) participants. Noninferiority of nAb response in vaccine-naïve versus vaccinated participants was the primary objective. The day-28 GMT ratio and SRR (percentage of participants with a ≥ 4 -fold rise in antibody response from baseline) were measured, and safety was assessed.

Of the participants enrolled from 11 September 2023 to 15 November 2023, per-protocol sets included 306/338 (90.5%) vaccine-naïve and 309/332 (93.1%) vaccinated participants. At day 28, adjusted GMTs (95% CI) against XBB.1.5 in the vaccine-naïve and vaccinated groups were 1491.5 (1277.5–1741.4) and 841.4 (723.9–978.0), respectively. The vaccine-naïve–vaccinated nAb GMTR was 1.8 (95% CI 1.43–2.20) and SRRs were 74.3% and 64.3% for vaccine-naïve and vaccinated participants, respectively (SRR difference: 10.0 [95% CI 2.6–17.4]). No new safety signals or events of special interest were reported.

A single dose of NVX-CoV2601 in vaccine-naïve participants with a history of SARS-CoV-2 infection elicited a robust nAb response that was noninferior to that observed in vaccinated participants. The vaccine was well-tolerated. These data support the use of NVX-CoV2601 as a single dose, regardless of prior vaccination history.

Tina DL, Ndhere DA. Safety and immunogenicity of Pfizer-BioNTech mRNA vaccine and Novavax NVX-CoV2373 COVID-19 mix and match booster vaccination in adolescents aged 12–17 years with HIV infection in Kenya. *Int J Infect Dis.* 2025;152 Suppl:107716. (18)

The trial evaluated the safety and immunogenicity of two COVID-19 vaccines in adolescents 12-17 years with HIV in Kenya. Adolescents who received homologous Ministry of Health primary vaccination platform with mRNA COVID-19 vaccines, were randomized 1:1 to receive a homologous or heterologous single booster dose of either Pfizer BioNTech mRNA COVID-19 Vaccine or Novavax NVX-CoV2373 Protein Sub-Unit COVID-19 vaccine. The primary objectives included: reactogenicity assessment for seven days post vaccination, occurrence of SAEs throughout the trial from booster vaccination and assessment of SARS-CoV-2 neutralization antibody titers and IgG antibodies at day 28.

There were 300 adolescents enrolled with similar baseline characteristics between study arms. The mean age was 15 years with a similar distribution between males and females. For local AEs, 206/300 (69%) participants reported at least one local AE (Vaccine A: 105/150 (70%) and vaccine B: 101/150 (67%). The most common local AE was mild pain. Other local AEs included itchiness, redness, and swelling. Importantly, Grade 3 or Grade 4 local AEs were reported for either vaccine. For systemic AEs, 170/300 (57%) participants reported at least one systemic AE (Vaccine A: 87/150 (58%) and vaccine B: 83/150 (55%)). The most common systemic AE was fatigue, followed by muscle ache and headache. A few participants reported diarrhea, nausea and vomiting. There were eight Grade 3 fevers, one Grade 3 fatigue, and four reported Grade 3 headaches with no life-threatening systemic AEs. There were 14 SAEs with none of which resulted in death.

On immunogenicity, there was a significant rise in SARS-CoV-2rS Protein IgG Antibody titers at Day 28, shown by GMRs: (Vaccine A, 6.23 [95% CI: 4.95 - 7.83] Versus Vaccine B, 3.60 [95% CI: 2.89 - 4.48] ($p < 0.0001$)). The GMRs were sustained at >1 at Day 85 but with values lower compared to Day 28.

It was demonstrated that both local and systemic AEs were mostly mild in nature. Vaccine A consistently elicited a stronger immune response compared with Vaccine A across all time points. Enzyme-Linked Immunosorbent Assay (ELISA) and neutralization assay results showed both vaccines increased antibody levels

Killander MI, Hedberg P, Wagner P, Lindahl H, Nystrom S, Blixt L, et al. Risk of COVID-19 hospitalisation by HIV-status and SARS-CoV-2 vaccination status during pre- and post-Omicron era in a national register-based cohort study in Sweden. *Infect Dis (Lond).* 2025 Feb;57(2):178-91. (19)

This nationwide registry-based study included all resident in Sweden ≥ 18 years with a positive SARS-CoV-2 PCR test during January 2021–February 2023. We estimated adjusted odds ratios (adjORs) for COVID-19 hospitalization and severe COVID-19 (Intensive Care Unit admission and 90-day mortality), categorized by SARS-CoV-2 vaccination status (0–1, 2, and ≥ 3 doses), and HIV-status.

Analyses were then categorized by time periods of pre-Omicron, Omicron during public testing, and Omicron after public testing.

A total of 1348 PLHIV and 1 669 389 people without human immunodeficiency virus (PWoH) were included. The PLHIV were older, more migrant (65 Versus 22%) and male (59 Versus 46%). Of PLHIV, 96% were on antiretroviral treatment and 94% virally suppressed. The adjORs of COVID-19 hospitalization were similar irrespective of HIV-status, controlled for demographics, calendar month of infection, comorbidities, and income. The PLHIV were more likely to be hospitalized than PWoH during Omicron and public testing (adjOR 2.3, 95% CI 1.1–4.2), but not after public testing. The odds of severe COVID-19 were three times higher in PLHIV compared to PWoH vaccinated with two doses (adjOR 3.2, 95% CI 1.3–6.9), but not when vaccinated with ≥ 3 doses (adjOR 0.7, 95% CI 0.2–1.6). Migrant and low nadir CD4⁺ T-cells were associated with higher odds of hospitalization in unvaccinated PLHIV.

This nationwide study, including mostly well-treated PLHIV, highlights the importance of vaccination with booster dose(s) for effective protection against severe COVID-19 in PLHIV. The PLHIV compared to PWoH did not have higher odds of COVID-19 hospitalization irrespective of SARS-CoV-2 vaccination status (0-1 dose, 2 doses, ≥ 3 doses) when adjusting for known risk factors including comorbidities and socioeconomic status.

Gwak E, Choe SA, Kim K, Bolormaa E, Fix J, Vadivale M, et al. Real-world effectiveness of NVX-CoV2373 and BNT162b2 mRNA COVID-19 vaccination in South Korea. Vaccine. 2025 Aug 30;62:127496. (20)

This retrospective study identified NVX-CoV2373 and BNT162b2 recipients aged ≥ 12 years from the Korea Disease Control and Prevention Agency-COVID-19-National Health Insurance Service database. Vaccine groups were propensity score-matched based on demographic characteristics, Seoul capital area residence, income level, comorbidity/disability, prior SARS-CoV-2 infection, and prior vaccination dose/timing. Outcomes were any and severe (intensive-care-unit admission or death within eight weeks of infection) laboratory-confirmed SARS-CoV-2 infection assessed from seven days after the third and fourth dose. Adjusted hazard ratios (aHRs) from matched groups measured vaccine effectiveness up to a 180-day risk window.

From February to December 2022, 923 833 NVX-CoV2373 and 1 286 604 BNT162b2 doses were administered. The 180-day risk-window aHRs (95% CI) for NVX-CoV2373 compared with BNT162b2 for any SARS-CoV-2 infection were 0.78 (0.76-0.79) post third dose and 0.86 (0.86-0.87) post fourth dose. The 180-day aHRs (95% CI) for severe infection were 0.73 (0.53-1.00) after the third dose and 1.21 (1.03-1.42) after the fourth dose.

NVX-CoV2373 demonstrated favorable and similar effectiveness against any and severe SARS-CoV-2 infection, respectively, compared with BNT162b2, with evidence of enhanced NVX-CoV2373 durability.

Vaccine failure is discussed in detail in Section 15.1.

17.3 CHARACTERIZATION OF BENEFITS

No new relevant efficacy findings in approved indications were identified during the reporting interval, and the efficacy profile of COVID-19 vaccine is unchanged.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1 BENEFIT-RISK CONTEXT - MEDICAL NEED AND IMPORTANT ALTERNATIVES

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. The virus rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In February 2020, the WHO designated the disease COVID-19. The virus that causes COVID-19 was designated SARS-CoV-2.

As of 02 February 2025, over 777.4 million confirmed cases and over seven million deaths have been reported globally (21). The reported case counts underestimate the overall burden of SARS-CoV-2, as only a fraction of acute infections is diagnosed and reported. Seroprevalence surveys in the US and Europe suggested that after accounting for potential false positives or negatives, the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, may exceed the incidence of reported cases by approximately 10-fold or more (22), (23).

Treatment Options:

Management of Persons with COVID-19:

Management of COVID-19 is based on the best supportive care and emerging standard of care. Medications authorized for treatment of COVID-19 in the EU include antiviral medicines (ie, Paxlovid® and Veklury®), monoclonal antibodies (ie, Gohibic®, Kavigale®, Regkirona®, RoActemra®, Ronapreve®, Xevudy®), and an immunosuppressive medicine (Kineret®) (24).

Prophylaxis:

The following vaccines are authorized for use in the EU for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus: Comirnaty® (BioNTech and Pfizer), Spikevax® (Moderna), Nuvaxovid (Novavax), Bimervax® (HIPRA Human Health), and Kostaive® (Seqirus). In addition, one monoclonal antibody, Ronapreve, is authorized for prevention of COVID-19. General preventative measures include social distancing, face masks, and proper hygiene (24).

18.2 BENEFIT-RISK ANALYSIS EVALUATION

18.2.1 Methodology

The current benefit-risk evaluation, for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older, is based on the pivotal studies (interventional clinical trials and non-interventional post-authorization studies) and all postmarketing data. New information that has become available during the reporting interval, including newly identified risks described in Section 16.2 and newly identified efficacy data described in Section 17.2, has been assessed to determine whether it affects the previously established benefit-risk profile of COVID-19 vaccine in the approved indication(s).

18.2.2 Benefit-risk evaluation

Benefit:

It has been six years since SARS-CoV-2 was declared a global pandemic by WHO. Several vaccines against the prototype Wuhan-Hu-1 strain had received authorizations/approvals globally as of late 2020/early 2021. Despite this vaccination number, there remains a large global need for additional vaccine doses, including vaccines efficacious against the evolving variants and having more readily satisfied storage conditions and stability.

In adult participants ≥ 18 years of age following primary series vaccination, NVX-CoV2373 demonstrated efficacy of $\sim 90\%$ in the pivotal Phase 3 study following primary vaccination, with comparable efficacy against variants that were either considered VOC/VOI or not considered VOC/VOI. Among NVX CoV2373 adult recipients, there were no cases of severe disease with an onset from at least seven days after second vaccination in the pivotal Phase 3 study. The clinical benefit of NVX CoV2373 was consistent among, males and females, White and non-White, Black or African Americans, and those with co morbidities or at high-risk of being exposed or infected with SARS-CoV-2. The results of the pivotal efficacy study demonstrating $\sim 90\%$ efficacy against mild, moderate, or severe COVID-19, as well as 100% efficacy against severe disease, are supported by the robust immune responses observed in the pivotal Phase 3 study. In older adults, nAb responses would have met the GMT non-inferiority criterion compared to adults 50 to < 65 years of age, an age group in which there were sufficient cases of COVID-19 to establish efficacy.

In adolescent participants 12 to < 18 years of age, based on the results of the Pediatric Expansion of the pivotal Phase 3 study 2019nCoV-301, NVX CoV2373 met the criteria to establish its effectiveness by demonstrating non-inferiority of the nAb response in adolescent participants 12 to < 18 years of age compared to young adults 18 to < 26 years of age following primary series vaccination. For the primary efficacy endpoint, the vaccine efficacy of NVX-CoV2373 for preventing symptomatic mild, moderate, or severe COVID-19 in baseline seronegative/ PCR negative adolescent participants was $\sim 80\%$ during a period in which the B.1.617.2 (Delta) variant was predominant. NVX-CoV2373 also generated

robust immune responses (nAb and anti-spike protein IgG) relative to placebo in adolescent participants 12 to <18 years of age regardless of baseline serostatus.

Risks:

Based on the administration of NVX-CoV2373 to 26,106 adults in the Adult Main study of Clinical Study 2019nCoV-301 across the initial and blinded crossover vaccination periods, with 13 353 participants receiving a booster vaccination and an additional 15 440 participants across the supportive clinical studies in the SARS-CoV-2rS clinical development program and 2153 adolescents in the Pediatric Expansion of Clinical Study 2019nCoV-301 across the initial and blinded crossover vaccination periods, with 1499 participants receiving a booster vaccination, following primary series vaccination or a heterologous/homologous booster vaccination, the safety profile has been largely characterized by mild or moderate reactogenicity reactions of short duration (median duration of two days). Most common among these reactions were tenderness and pain at the injection site and systemic events of fatigue, muscle pain, headache, joint pain, and malaise. Although the incidence of unsolicited TEAEs in adult participants and of unsolicited treatment-related TEAEs in both adult and adolescent participants was slightly higher in the NVX-CoV2373 group than in the placebo group, the difference was largely due to reactogenicity-like events. The SAEs and deaths (adults only) occurred in few participants, with similar events for placebo and vaccine recipients that were generally balanced across treatment groups for both adults and adolescents. These findings are further supported with the data from the Integrated Safety Summary, which comprised 31 479 adult participants and 1487 adolescent participants in the NVX-CoV2373 groups who received study vaccine at the start of each clinical study. The safety profile of NVX-CoV2515 (BA.1), NVX-CoV2540 (BA.5), NVX-CoV2601 (XBB.1.5), and NVX-CoV2705 (JN.1) was consistent with the safety observations and conclusions reported following NVX-CoV2373 administration.

Anaphylaxis and Myocarditis and/or pericarditis are important identified risks; and VAED including VAERD, Atrial fibrillation and/or Atrial flutter, Cerebrovascular Accident, Cranial Nerve VIII Disorders (including Vestibular Neuronitis), Ocular Motor Cranial Nerve Disorders (ie, Cranial Nerve Disorders Affecting Cranial Nerves III, IV, or VI) are important potential risks associated with the use of COVID-19 vaccine and have been reported at low reporting rate as presented in the tables for risk characterization.

Benefit-risk conclusion:

Based on the totality of the data across the SARS-CoV-2rS clinical development program, COVID-19 vaccine administered as either two intramuscular injections at least 21 days (+ 7 days) apart as primary series vaccination or as one intramuscular injection in previously vaccinated individuals is an effective vaccine with an acceptable safety profile for the active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in both adults ≥ 18 years of age and adolescents 12 to <18 years of age.

Homologous booster vaccination in adult and adolescent participants induced robust immune responses that exceeded those reported following primary series vaccination. Heterologous booster vaccination in adult participants also resulted in robust increases in nAb titers.

It is important to note that the dose of COVID-19 vaccine for both primary and booster injections is the same for all ages, thus facilitating ease of use for vaccine administrators and reducing the likelihood of dosing errors.

Overall, the benefit-risk ratio of COVID-19 vaccine remains positive for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older under the current recommended conditions of use.

19 CONCLUSIONS AND ACTIONS

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older remains positive in the currently approved conditions of use.

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