Summary of the Swiss Risk Management Plan (RMP) for Nuvaxovid, COVID-19 VACCINE (RECOMBINANT, ADJUVANTED)

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Name of the Marketing Authorization Holder: Future Health Pharma GmbH

Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Nuvaxovid is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Nuvaxovid in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Future Health GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Nuvaxovid.

SUMMARY OF RISK MANAGEMENT PLAN FOR NUVAXOVID (COVID-19 VACCINE (RECOMBINANT, ADJUVANTED))

This is a summary of the RMP for Nuvaxovid. The RMP details important risks of Nuvaxovid, how these risks can be minimised, and how more information will be obtained about Nuvaxovid's risks and uncertainties (missing information).

Nuvaxovid's SmPC and its package leaflet give essential information to HCPs and patients on how Nuvaxovid should be used.

This summary of the RMP for Nuvaxovid should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Nuvaxovid RMP.

I. The medicine and what it is used for

Nuvaxovid is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older (see SmPC for the full indication). It contains SARS-CoV-2 spike protein and is adjuvanted with Matrix-M as the active substance and it is given by intramuscular (IM) injection.

Further information about the evaluation of Nuvaxovid's benefits can be found in Nuvaxovid's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/nuvaxovid.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nuvaxovid, together with measures to minimise such risks and the proposed studies for learning more about Nuvaxovid risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and monthly Summary Safety Reports so that immediate action can be taken as necessary. These measures constitute routine PV activities.

If important information that may affect the safe use of Nuvaxovid is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nuvaxovid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nuvaxovid. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

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

II.B Summary of important risks

Important identified risk: Myocarditis and/or pericarditis	
Evidence for linking the risk to the medicine	Literature on COVID-19 vaccines, post-market safety data, and clinical trial data.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk. Immunocompromised patients may be at a higher risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 and 4.8. PL section 2. <u>Additional risk minimisation measures:</u> None

Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022 Study 2019nCoV-501; final CSR estimated date 31 December 2022 Study 2019nCoV-302; final CSR estimated date 31 December 2022 Study 2019nCoV-505; final CSR estimated date 31 May 2023 Study 2019nCoV-311; final CSR estimated date 31 July 2023 Study 2019nCoV-301; final CSR estimated date 31 Dec 2023 **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	
Evidence for linking the risk to the medicine	Literature on viral vaccines, safety information of other COVID-19 vaccines, clinical trials. Vaccine-associated enhanced disease (VAED) has been rarely encountered with existing vaccines or viral infections. It was observed in children given formalin-inactivated whole-virus vaccines against RSV and measles virus. No events of VAED/VAERD have been reported in the current Nuvaxovid 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.
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 (Lambert 2020). Population-based surveillance might give more insight in this, should any VAED occur.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: **Ongoing clinical trials** Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022 Study 2019nCoV-501; final CSR estimated date 31 December 2022 Study 2019nCoV-302; final CSR estimated date 31 December 2022 Study 2019nCoV-505; final CSR estimated date 31 May 2023 Study 2019nCoV-311; final CSR estimated date 31 July 2023 Study 2019nCoV-301; final CSR estimated date 31 December 2023 **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

Important missing information: Use in pregnancy and while breastfeeding	
Evidence for linking the risk to the medicine	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/foetal development, parturition, or post-natal development. Administration of Nuvaxovid in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Breastfeeding It is unknown whether Nuvaxovid is excreted in human milk. Fertility Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Risk factors and risk groups	Pregnant and breastfeeding women
Risk minimisation measures	Routine risk communication: SmPC Sections 4.6 and 5.3 PL Section 2 Additional risk minimisation: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study 2019nCoV-405 (Pregnancy and infant outcomes safety study using the "COVID-19 Vaccines International Pregnancy Exposure Registry" (C-VIPER)); final study report estimated date 30 June 2027

Important missing information: Use in immunocompromised patients	
Evidence for linking the risk to the medicine	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 were enrolled in the 2019nCoV-501 study. The safety profile of Nuvaxovid 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 Nuvaxovid will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded.
Risk factors and risk groups	Individuals with compromised immune function due to acquired or genetic conditions or conditions requiring the use of immunosuppressants
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** Study 2019nCoV-501; final CSR estimated date 31 December 2022 Study 2019nCoV-302; final CSR estimated date 31 December 2022 Study 2019nCoV-505; final CSR estimated date 31 May 2023 Study 2019nCoV-301; final CSR estimated date 31 December 2023 **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

Important missing information: Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	
Evidence for linking the risk to the medicine	The vaccine has not been studied in frail individuals with comorbidities that may compromise immune function due to the condition or treatment of the condition. Frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, 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 Nuvaxovid will be different to that of the general population, but given the paucity of data, the possibility cannot be excluded
Risk factors and risk groups	Frail individuals with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), obesity defined as BMI $\geq$ 30 kg/m^2, DM2, cardiovascular disease, chronic kidney disease or HIV).
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

Important missing information: Use in patients with autoimmune or inflammatory disorders	
Evidence for linking the risk to the medicine	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders. There is no evidence from Nuvaxovid 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.
Risk factors and risk groups	Patients with autoimmune or inflammatory disorders
Risk minimisation measures	Routine risk minimisation measures: PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 Sep 2025

Important missing information: Interaction with other vaccines	
Evidence for linking the risk to the medicine	There is limited information on the safety of the vaccine when administered other vaccines within 28 days prior to the first dose or any dose of Nuvaxovid, except for seasonal influenza vaccine, <14 days. Approximately 400 participants were concomitantly administered a seasonal influenza vaccine with Nuvaxovid or placebo. The binding antibody response to SARS-CoV-2 was lower when Nuvaxovid was given concomitantly with inactivated influenza vaccine. The clinical significance of this is unknown.
Risk factors and risk groups	Individuals who will receive other vaccines within 28 prior to 14 days after immunisation with Nuvaxovid.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 and 5.1 PL section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** Study 2019nCoV-302; final CSR estimated date 31 December 2022 **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

Important missing information: Long-term safety	
Evidence for linking the risk to the medicine	Understanding of the long-term safety profile of Nuvaxovid is currently limited. The median duration of safety follow-up in each of the 2 Phase 3 studies was at least 60 days. Follow-up was conducted for one year post-vaccination (Studies 101 Part 1 and 2, 501, and 302) or 2 years post-vaccination (Study 301).
Risk factors and risk groups	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
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: **Ongoing clinical trials** Study 2019nCoV-101 (Part 2); final CSR estimated date 31 December 2022 Study 2019nCoV-501; final CSR estimated date 31 December 2022 Study 2019nCoV-302; final CSR estimated date 31 December 2022 Study 2019nCoV-311; final CSR estimated date 31 July 2023 Study 2019nCoV-301; final CSR estimated date 31 December 2023 **Post-authorisation studies** Study 2019nCoV-402 (Safety study using the UK CPRD database); final study report estimated date 30 June 2025 Study 2019nCoV-404 (Safety study using a US-based claims and/or electronic health records (EHR) database); final study report estimated date 30 September 2025

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Nuvaxovid.

II.C.2 Other studies in post-authorisation development plan

Study: **2019nCoV-101 (Part 2)**

Purpose of the study:

To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with or without Matrix-M adjuvant in healthy subjects.

Study: **2019nCoV-501**

Purpose of the study:

To evaluate the efficacy, immunogenicity, and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in South African adult subjects living without HIV; and safety and immunogenicity in adults living with HIV.

Study: **2019nCoV-302**

Purpose of the study:

To demonstrate the efficacy of SARS-CoV-2 rS with Matrix-M adjuvant in the prevention of virologically confirmed (by PCR to SARS-CoV-2), symptomatic COVID-19, when given as a two-dose vaccination regimen, as compared to placebo, in serologically negative (to SARS-CoV-2) adults.

Study: **2019nCoV-505**

Purpose of the study:

To evaluate the safety and immunogenicity of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M adjuvant in people living with HIV and without HIV.

Study: **2019nCoV-311**

Purpose of the study:

To evaluate the safety and immunogenicity of 2 booster doses of the monovalent prototype vaccine (NVX-CoV2373), monovalent Omicron subvariant vaccines (NVX-CoV2515 [BA.1] and NVX-CoV2540 [BA.5]) and bivalent vaccines (NVX-CoV2373 + NVX-CoV2515 and NVX-CoV2373 + NVX-CoV2540) participants who have already been immunized with 2 or 3 doses of the Moderna or Pfizer/BioNTech prototype vaccines. Additionally, the study will investigate the ability of the NVX-CoV2515 vaccine to demonstrate a statistically superior difference in the titers of cross-neutralizing antibodies and IgG antibodies compared to the NVX-CoV2373 prototype vaccine.

Study: **2019nCoV-301**

Purpose of the study:

To evaluate the efficacy of a two-dose regimen of SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo against symptomatic COVID-19 illness diagnosed ≥ 7 days after completion of the second injection in the initial set of vaccinations of adult participants ≥ 18 years of age. Evaluate the efficacy and safety after vaccination with SARS-CoV-2 rS adjuvanted with Matrix-M compared to placebo in paediatric participants 12 to <18 years of age. Evaluate the safety and immunogenicity following a single booster dose approximately 6 months following active vaccination in adults and adolescents. Evaluate the safety and immunogenicity following a second booster dose approximately 6 months following the first booster vaccination in a sub-study of adults enrolled in the study.

Study: **2019nCoV-402 (UK Post-Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD)**

Purpose of the study:

To evaluate whether there is an increased risk of select safety outcomes of interest following vaccination with the Nuvaxovid using a (i) a self-controlled case series (SCCS) design and (ii) a comparative cohort study design.

Study: **2019nCoV-405 (Global Pregnancy and Infant Outcomes Study Using the COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER))**

Purpose of the study:

To estimate the risk of obstetric outcomes and infant outcomes among pregnant women exposed to a single (homologous) or mixed (heterologous) Nuvaxovid series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring relative to a matched reference group who received no COVID-19 vaccinees during pregnancy.

Study: **2019nCoV-404 (US Post-authorisation safety study using a claims and/or EHR database)**

Purpose of the study:

To evaluate the risk of select AESIs following vaccination with at least one dose of the Novavax COVID-19 Vaccine using SCCS and cohort study designs.

Study: **2019-nCoV-401 (EU Post-Authorisation Effectiveness Study Based on a Test-Negative Design Using the COVIDRIVE Platform)**

Purpose of the study:

To estimate COVID-19 vaccine effectiveness (CVE) of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have completed their primary vaccination series, compared to unvaccinated patients. Additionally, the study will estimate CVE of Nuvaxovid against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine compared to a) unvaccinated patients and b) patients who previously completed at least a primary series with any COVID-19 vaccine but did not receive the last additional dose. Further, the study will estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose, compared to unvaccinated patients.

Study: **2019nCoV-403 (US Post-authorisation Effectiveness Study Using a Claims and/or EHR Database)**

Purpose of the study:

To estimate the effectiveness of Nuvaxovid in preventing COVID-19 hospitalisations compared to unvaccinated individuals.