STUDY PROTOCOL

STUDY TITLE:	A follow-on study to assess the safety and immunogenicity of a booster dose of GBS-NN/NN2 vaccine, 1 to 5 years after GBS-NN/NN2 recipients in study MVX0002 have completed the primary vaccination course, in comparison with a single dose of GBS-NN/NN2 administered in placebo participants from study MVX0002 or vaccine naïve participants
STUDY NUMBER:	RD 751/34984 (MVX0003)
EudraCT NUMBER:	2021-000435-31
IRAS ID:	294826
INVESTIGATIONAL MEDICINAL PRODUCT(s):	Group B Streptococcus Vaccine (GBS-NN/NN2)
PLANNED STUDY DOSES:	A single intramuscular injection of GBS-NN/NN2 containing 50 µg of GBS-NN and 50 µg of GBS/NN2
PRINCIPAL INVESTIGATOR:	Dr Helen Philpott Simbec-Orion Merthyr Tydfil CF48 4DR UK Tel: [redacted] Fax: [redacted] Email: [redacted]
STUDY QUALIFIED PHYSICIAN:	N/A.
STUDY SPONSOR:	MinervaX ApS Ole Maaløes Vej 3 DK-2200 Copenhagen N Denmark
SPONSOR'S RESPONSIBLE PHYSICIAN:	Dr Geoff Kitson CMO (Consultant) ProPharma Partners Limited 2nd Floor Afon Building Worthing Road Horsham RH12 1TL UK Tel: [redacted] Mobile: [redacted] Email: gkitson@propharmapartners.co.uk Out of hours: [redacted]

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SAFETY LABORATORIES/ANALYSIS OF ANTIBODIES SPECIFIC FOR GBS-NN/NN2/DATA MANAGEMENT/STATISTICAL ANALYSIS/MEDICAL MONITORING
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PROTOCOL FINALISATION STATEMENT

This protocol is not considered final unless accompanied by an approval letter from the Research Ethics Committee and Notice of Acceptance from the relevant Competent Authority.

Protocol Prepared by: LT

1 SIGNATURE PAGE

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made if necessary, to protect the safety, rights or welfare of the participants.

STUDY SPONSOR:

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Date:

DocuSigned by:
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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 21-Jan-2022 | 06:24 CET
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PRINCIPAL INVESTIGATOR:

Dr Helen Philpott
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Signing Time: 20-Jan-2022 | 15:27 GMT
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2 PROTOCOL AMENDMENT/REVISION HISTORY

Protocol Version/ Date	Type of Amendment	Amendment Rationale	Sections Affected	Summary of Amendment / Changes to the Protocol
V1.0, 19 April 2021	N/A	N/A	N/A	N/A
V2.0, 03 June 2021	N/A	Response to Ethics Provisional Opinion Queries	Protocol Front Page	- Study title updated to reflect data comparisons to be made between previously vaccinated participants and vaccine naïve participants as per REC request.
			Section 3 – Protocol Synopsis	- Synopsis updated to align with changes in main body text.
			Section 7.1. – Study Personnel	- Personnel field for statistics updated to 'Simbec-Orion Biometrics'.
			Section 8.2. – Rationale for Study	- Section text updated to include rationale for the inclusion of vaccine naïve participants as per REC request.
			Section 9 – Study Objectives	- All primary and secondary objectives updated to reflect data comparisons to be made between previously vaccinated participants and vaccine naïve participants as per REC request.
			Section 10.1. – Overall Study Design and Plan	- Section text updated to reference a first vaccine dose for vaccine naïve participants as per REC request.

			Section 10.3. – Discussion of Study Design, including the choice of Control Groups Section 10.7.1.4.1. - Adverse Events Table 10.8.1. – Summary of Source Documentation Location Section 10.9.2. – Study Variables/ Endpoints	- Section text updated to include rationale for the inclusion of vaccine naïve participants as per REC request. - Adverse event causality definitions updated in line with latest protocol template. - Table updated in line with latest protocol template. - All primary and secondary endpoints updated to reflect booster and first dose data comparisons to be made between previously vaccinated participants and vaccine naïve participants as per REC request.
V3.0, 09 July 2021	N/A	Response to MHRA Grounds for Non-Acceptance	Section 3 – Protocol Synopsis Section 8.6 – Reference Safety Information Section 10.2 – General Stopping Criteria	- Synopsis updated to align with changes in main body text. - Section updated to remove reference to non-serious adverse events for RSI as per MHRA request. - Section text updated to include global temporary halt criteria as per MHRA request.

			Section 10.4.1 – Inclusion Criteria	- Inclusion criteria #4-#7 updated to include clear definitions for females of childbearing and non-childbearing potential as per MHRA request.
			Section 10.4.2 – Exclusion Criteria	- New exclusion criterion #3 added and exclusion criterion #15 updated to revise use of prior and concomitant medication as per MHRA request.
			Section 10.5.1 – Contraception	-Contraception requirements updated to reflect CTFG guidance for highly effective methods as per MHRA request.
			Section 10.6.10.1 – Prior Medication	- Prior medication restrictions updated to restrict use of medications in vaccine naïve participants and those MVX0002 participants who do not have new medical conditions which require the use of permitted chronic medications as per MHRA request.
			Section 10.6.10.2 – Concomitant Therapy	-Concomitant medication restrictions updated to restrict use of medications in vaccine naïve participants and those MVX0002 participants who do not have new medical

				conditions which require the use of permitted chronic medications as per MHRA request.
			Table 10.7.1 – Study Flow Chart	- Flow chart updated to include laboratory safety testing and brief physical examinations on Day 8 & Day 29 as per MHRA request.
			Table 10.7.2 – Summary of Blood Volume	- Blood volume table and overall blood volume updated to reflect the addition of 2 laboratory safety tests on Day 8 and Day 29 as per MHRA request.
V4.0, 23 August 2021	NSA01	Protocol Template update	Title page	Change in PI telephone number.
			Section 5 - Abbreviations used in the protocol text.	Addition of serious adverse drug reaction (SAR).
			Section 10.6.1 - Identity	Removal of reference to placebo.
			Section 10.6.2 - Receipt and Storage	Changes to IMP storage details and reference to SOPs.
			Section 10.07.1.4.1 -Adverse Events	Change reporting after follow-up to include SARs and for reports to be sent to Diamond (PV) not sponsor.
			Section 10.07.1.4.2 - Laboratory Safety Assessments	Reference to possibility of referral laboratory to analyse Laboratory Safety Assessments.

			Section 10.7.2 Summary of Blood Volumes Section 10.7.5.2 - Additional Exploratory Pharmacodynamic Assessments Throughout the protocol	Removal of footnote "From the biochemistry blood sample collected at the post-study follow-up visit, the serum pregnancy test will be analysed from the same serum sample" as it is a urine pregnancy test at post-study. Changed shipping address for [redacted] samples. "PD [redacted] samples amended to "Exploratory [redacted] samples" Administrative changes.
V5.0 20 Jan 2022	NSA02	Covid-19 testing method update	Inclusion criteria in the Synopsis and Section 10.4.1 (Inclusion Criteria), Section 10.7.1.1.4 (Covid-19 testing)	Inclusion criteria 14 has been changed from 'Participants with a negative COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) test on admission (Day 1 or Day-1 if deemed appropriate by the Principal Investigator (PI)) if required at the time.' to 'Participants with a negative COVID-19 test on admission (Day 1 or Day-1 if deemed appropriate by the Principal Investigator (PI)) if required at the time.' Section 10.7.1.1.4 (Covid-19 testing) has

				been amended to 'A nasopharyngeal and/or oropharyngeal swab will be collected. COVID-19 testing will be routinely performed via lateral flow test or real time polymerase chain reaction as deemed appropriate by the Principal Investigator.'

3 SYNOPSIS

NAME OF COMPANY: MinervaX ApS

NAME OF INVESTIGATIONAL MEDICINAL PRODUCT: Group B Streptococcus Vaccine (GBS-NN/NN2)

NAME OF ACTIVE INGREDIENT: GBS-NN and GBS-NN2

TITLE OF STUDY: A follow-on study to assess the safety and immunogenicity of a booster dose of GBS-NN/NN2 vaccine, 1 to 5 years after GBS-NN/NN2 recipients in study MVX0002 have completed the primary vaccination course, in comparison with a single dose of GBS-NN/NN2 administered in placebo participants from study MVX0002 or vaccine naïve participants

PRINCIPAL INVESTIGATOR: Dr Helen Philpott

STUDY CENTRE: Simbec-Orion Clinical Pharmacology
Merthyr Tydfil, CF48 4DR, UK

CLINICAL PHASE: I

OBJECTIVES:

Primary Objective

- To evaluate the safety over 12 weeks of a single booster dose of the GBS vaccine GBS-NN/NN2, administered 1 to 5 years after completion of the initial primary vaccination course and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants).

Secondary Objectives

- Safety Objectives: To evaluate the long-term safety profile of the GBS-NN/NN2 vaccine 6 months following the booster dose in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.
- Immunological Objectives:
  - To evaluate the IgG antibody responses, specific to GBS-NN and GBS-NN2 fusion proteins, on Day 1 and Day 85 in previously vaccinated healthy female participants and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.
  - To evaluate the IgG antibody responses, specific to AlpCN, RibN, Alp1N and Alp2-3N, on days 1, 8, 29, 57, 85 and 183, in previously vaccinated healthy female participants and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.

Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]

METHODOLOGY:

This is an open label vaccine booster follow-up study. Participants who had received a primary course of GBS-NN/NN2 or placebo in Study MVX0002 will be invited to return to receive a booster dose (or first dose in the case of placebo or vaccine naïve participants) 1 to 5 years after the completion of the primary course of vaccination. All participants will receive a single dose of GBS-NN/NN2 containing 50µg of each fusion protein.

A minimum of 30 and a maximum of 40 female participants will be recruited, comprised of between 20 and 30 participants who had received previous vaccination with GBS-NN/NN2 in the MVX0002 study and up to 10 participants who had received placebo in the MVX0002 study. If an insufficient number of previous placebo recipient participants return to this study, vaccine naïve participants will be recruited.

The study will include 7 visits (Visit 1: Screening Period, Visits 2-6: Treatment Period and Visit 7: Post-study Follow-up).

Visit 1 - Screening Period (Day -28 to Day -1):

After signing the informed consent form, Screening assessments will be performed within 28 days of the planned dose to ensure the eligibility of participants. Screening assessments will include:

- Inclusion/Exclusion Criteria
- Demographic data
- Subject number and Investigational Medicinal Product received in MXV0002 study
- Medical history
- Physical examination (full)
- Height, weight and body mass index (BMI)
- Vital signs (supine heart rate, blood pressure, tympanic temperature and respiration rate)
- 12-lead ECG
- Virology (human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab)
- Laboratory safety tests (biochemistry, haematology)
- Urinalysis
- Urine drugs of abuse including alcohol and cotinine
- Serum pregnancy test
- Follicle Stimulating Hormone Test (Postmenopausal women only)
- Prior and concomitant medication

Visits 2-6 - Treatment Period (Day 1 to Day 85):

Visit 2 (Day 1):

Participants will be admitted to the clinic in the morning of Day 1 and will remain in the unit until the 30 minutes (min) post-dose scheduled assessments. The following procedures will be performed on Day 1.

- COVID-19 Reverse Transcription Polymerase Chain Reaction Test: Pre-dose (can be performed at Visit 1, Day -1 at the discretion of the Principal Investigator (PI))
- Physical examination: Pre-dose (brief) and 30 min (± 5 min) post-dose (Symptom-Directed Physical Examination prior to discharge)
- Vital signs: Pre-dose and 30 mins (±5 min) post dose
- Urine pregnancy test: Pre-dose
- Urine drugs of abuse (DOA) including alcohol and cotinine: Pre-dose
- Review of participant eligibility: Pre-dose
- Pharmacodynamic (PD) blood sample (antibody response): Pre-dose
- Exploratory blood sample ([redacted]): Pre-dose
- Administration of investigational vaccine
- Assessment of injection site: Pre-dose and 30 min (±5 min) post-dose. Photographs may be taken of injection site reactions, as required
- Adverse event (AE) check
- Concomitant medication check
- Participants receive Participant Diary Card Day 1 to Day 7 to record temperatures, injection site reactions, general reactions, AEs and concomitant medication check from the evening of Day 1 to the evening of Day 7.

Visit 3 (Day 8 ± 1 days), Visit 4 (Day 29 ± 2 days), Visit 5 (Day 57 ± 2 days) and Visit 6 (Day 85 ± 5 days):

The following procedures will be performed:

- Vital signs
- Laboratory safety tests (biochemistry and haematology): Visit 3 (Day 8), Visit 4 (Day 29) & Visit 5 (Day 57)

- Brief physical examination: Visit 3 (Day 8) & Visit 4 (Day 29)* may also be performed at any other time point as clinically indicated
- PD blood sample (antibody response)
- Exploratory blood sample ([redacted]): Visit 3 (Day 8) only
- Assessment of injection site: Photographs may be taken of injection site reactions, as required.
- AE check
- Concomitant medication check
- Blood samples for future validation and calibration work will be collected on Day 29, Day 57 and Day 85
- Review of Participant Diary Card Day 1 to Day 7
- Participants receive Participant Diary Card Day 85 to Day 183 to record AEs and concomitant medication

Visit 7: Post Study Follow-Up (Day 183 ±7 days):

A post study follow-up visit will take place on Day 183 (±7 days) to ensure the ongoing wellbeing of the participants. The following procedures will be performed:

- Physical examination (brief)
- Vital signs
- Laboratory safety tests (biochemistry, haematology)
- Urinalysis
- Urine pregnancy test
- PD blood sample (antibody response)
- AE check
- Concomitant medication check
- Review of Participant Diary Card Day 85 to Day 183

If all follow-up assessments are satisfactory to the PI (or deputy), participants will be discharged from the study. If any AEs are ongoing, or any assessments are not satisfactory, participants may be recalled to the unit for follow-up assessments until the PI/deputy is satisfied and the subject may be discharged from the study. Participants will be advised to return or contact the unit at any time if they think they may be experiencing any AEs.

NUMBER OF PARTICIPANTS:

A minimum of 30 and a maximum of 40 female participants will be recruited.

- Between 20 and 30 participants who had received previous vaccination with GBS-NN/NN2 in the MVX0002 study.
- Up to 10 participants who had received placebo in the MVX0002 study. If an insufficient number of previous placebo recipient participants return to this study, vaccine naïve participants will be recruited.

MAIN INCLUSION CRITERIA:

1. Women who have participated in study MVX0002, with GBS-NN/NN2 vaccine and received active vaccine or placebo (unless it is necessary to recruit vaccine naïve participants to bolster the number of participants who received placebo in MVX0002).
2. Able to voluntarily provide written informed consent to participate in the study.
3. Healthy female participants aged 18-40 years (vaccine naïve participants only).
4. Female participant of childbearing potential willing to use a highly effective method of contraception (in addition to a condom for male partners), if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from the first dose until completion of the Day 85 visit. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. For the purposes of this study, this definition of a female

of childbearing potential applies to all females in the study i.e., those who participated in the MVX0002 study and those who are considered vaccine naïve.

5. Female participant of non-childbearing potential. For the purposes of this study, this is defined as the participant being at least 4 months post-surgical sterilisation (including bilateral fallopian tube ligation or bilateral oophorectomy with or without hysterectomy).
6. Female participant with a negative pregnancy test at Screening and prior to dose.
7. Female participant of menopausal status confirmed by demonstrating at Screening that the serum level of the follicle stimulating hormone (FSH) falls within the respective pathology reference range. In the event a participant's menopausal status has been clearly established (for example, the participant indicates she has been amenorrhoeic for 10 years, confirmed by medical history, etc), but serum FSH levels are not consistent with a postmenopausal status, determination of the participant's eligibility to be included in the study will be at the Investigator's discretion following consultation with the Sponsor.
8. Body mass index (BMI) ≥18 and ≤30 kg/m2 (vaccine naïve participants only).
9. Participants' weight ≥ 50 kg and ≤ 100 kg at Screening (vaccine naïve participants only).
10. Non-smokers for at least 3 months prior to study vaccine administration.
11. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before dose administration of the IMP.
12. Participants with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion, if on prescribed opiates resulting in a positive test, participants may be eligible at the investigators discretion).
13. No clinically significant abnormalities in vital signs (supine blood pressure/heart rate, respiration rate, tympanic temperature) determined within 28 days before dose of IMP.
14. Participants with a negative COVID-19 test on admission (Day 1 or Day-1 if deemed appropriate by the Principal Investigator (PI)) if required at the time.

MAIN EXCLUSION CRITERIA:

1. Participants who have an autoimmune disease.
2. Participants who have a current infection or any significant illness at Screening (such participants can be rescreened once the active infection or significant illness has resolved).
3. Participants with history or presence of significant cardiovascular disease, pulmonary, hepatic, gallbladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, autoimmune disease or current infection.
4. Laboratory values at Screening which are deemed by the Investigator to be clinically significantly abnormal.
5. Positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab).
6. Participation in a clinical drug study during the 90 days or 5 half-lives, whichever is longer, preceding the initial dose in this study (such participants can be rescreened once the 90-day or 5 half-lives period has elapsed).
7. Participants with a history of severe allergic reactions after previous vaccination.
8. Participants with a history of hypersensitivity to the investigational medicinal product or any of the excipients within the IMP or documented allergy to aminoglycosides.
9. Participants who have received any vaccine within 7 days of dosing, or who are planning to receive a vaccine up to 7 days after receiving the GBS-NN/NN2 vaccine.
10. Participants who have received immunosuppressive therapy within the 6 months prior to Screening.
11. Participants with tattoos at the proposed site of vaccine administration.
12. Participants who, in the opinion of the Investigator, are unsuitable for participation in the study.
13. Pregnant or breast feeding.
14. Current or history of drug or alcohol abuse, or a positive urine alcohol test prior to dosing.

15. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP with the exception of contraceptives and paracetamol (*applies to vaccine naïve participants i.e., those who did not participate in the MVX0002 study and participants from the MVX0002 study (both active and placebo) who have not developed new medical conditions which require the use of chronic medications considered as permitted)*. If participants who participated in the MVX0002 study (either active or placebo recipients) have developed new medical conditions which require the use of chronic medications that do not affect the immune system, the inclusion of such participants will be permitted at the discretion of the Investigator on a case-by-case basis and, only if it is considered that the inclusion within the MVX0003 study will not be detrimental to participant safety.
16. Donation of blood or blood products within 90 days prior to vaccine administration.

INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION:

All participants will receive a single 0.5mL intramuscular injection of GBS-NN/NN2 containing 50 µg of GBS-NN and 50 µg of GBS/NN2.

- GBS-NN/NN2 vaccine will be supplied as a pre-mixed vial containing 0.35 mg/mL each of GBS-NN and GBS-NN2, to be adsorbed to Alhydrogel® adjuvant supplied separately.

Administration will be by intramuscular injection, preferably into the deltoid muscle of non-dominant arm. The dominant arm may be used if it is not possible to administer into the non-dominant arm *e.g.*, due to a tattoo.

STUDY VARIABLES/ENDPOINTS:

Primary Endpoints

The following endpoints will be evaluated to assess the safety over 12 weeks of a single booster dose of the GBS vaccine (GBS-NN/NN2): local and systemic reactogenicity; adverse events; laboratory tests; urinalysis; vital signs; physical examination.

Secondary Endpoints

- The following secondary safety endpoints will be evaluated to assess the long-term safety profile of the GBS-NN/NN2 vaccine 6 months following the dose: the incidence of autoimmune diseases and/or clinically relevant medical events related to the vaccination that occur in the 6-month follow-up period.
- The following secondary **immunological endpoints** will be evaluated.
    - Individual participant antibody concentration specific for GBS-NN and GBS-NN2, in µg/mL, at 0 and 84 days after the dose.
    - Individual participant antibody concentration specific for AlpCN, RibN, Alp1N and Alp2-3N, in µg/mL, at 0, 14, 28, 56, 84 and 182 days after the dose.

From the endpoints listed above the following will be derived:

- Geometric mean fold increase in antibody concentration, specific for GBS-NN and GBS-NN2, between Day 1 and Day 85.
- Geometric mean fold increase in antibody concentration, specific for AlpCN, RibN, Alp1N and Alp2-3N, between Day 1 and Days 8, 29, 57, 85 and 183.
- Proportion of participants achieving antibody concentrations, specific for AlpCN, RibN, Alp1N and Alp2-3N, above 0.5, 1, 2, 4 µg/mL, 7, 28, 56, 84 and 182 days after receiving the booster dose.
- The values of these endpoints 84 days after the dose will be the basis of the primary immunological analysis; this timepoint is anticipated to be the time of delivery after vaccination in a pregnant woman.

The secondary endpoints relating to antibody concentrations specific for AlpCN, RibN, Alp1N and Alp2-3N and all exploratory endpoints will be analysed and reported separately. Full details of the analyses will be documented in a separate plan(s). Comparisons will be made to the individual participants antibody concentration achieved on the previous study MVX0002.

The values of these endpoints on Day 85 will be the basis of the primary immunological analysis. This timepoint

is anticipated to be the time of delivery after vaccination in a pregnant woman.

STATISTICAL METHODS:

Details of the planned analyses will be described in the Statistical Analysis Plan. Statistical analyses will be performed by Simbec-Orion using SAS 9.4 or higher. Descriptive statistics for qualitative parameters will be provided using absolute frequencies (n) and relative frequencies (%). Inferential statistical tests will be carried out to compare results between treatment groups (received active or placebo in MVX0002 study/vaccine naïve), depending on studied variable type. The detailed analyses will be fully documented in the Statistical Analysis Plan.

Analysis Sets:

- **Safety Set (SAF):** All enrolled participants who receive the study vaccine will be included in the Safety Set. This analysis set will be used for baseline and safety summaries as well as for all study listings.
- **Immunogenicity Set (IG):** The subset of participants who will receive the study vaccine with available post-vaccination titres.
- **Per Protocol Set (PP):** All participants included in the IG Set who do not violate the protocol in a way that may invalidate or bias the results.

The immunological analyses will primarily be performed on the IG Set but will also be performed on the PP set if the number of participants in the PP set differs by more than 5% from that of the IG Set.

Demographic and Background Data:

All demographic and background data will be listed:

Disposition: Participant disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of participants dosed, completed and prematurely discontinued (including reason for discontinuation) from the study will be summarised. Additionally, the number and percentage of participants within each analysis set will be summarised.

Demographics: Demographic data will be listed. Descriptive statistics (number of participants in the analysis set (N), number of participants with non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum) will be tabulated for the continuous variables age, height, weight and BMI and frequencies (number and %) for the categorical variable race.

Demographic data will be listed and summarised using the Safety Set. Demographic characteristics will be presented for other analysis sets (Immunogenicity and/or Per Protocol sets) if they differ from the Safety Set.

Safety Data:

All safety data will be listed:

- **AEs:** All AEs occurring up to and including Day 85, including those which occurred prior to dose of Investigational Medicinal Product, will be listed.
- **Physical examinations**
- **Laboratory Safety Test:** biochemistry, haematology, and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges.
- **Vital Signs:** vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time point will be tabulated.
- **Injection Site Reactions:** a summary of injection site reactions will be produced by visit and category (redness, bruising, induration, itching and pain), including the number and percentage of participants in each category.

Pharmacodynamic Data:

Immunogenicity will be assessed using the Immunogenicity Set and will be repeated for the Per Protocol Set, should the analysis sets differ.

Antibody Response:

Antibody titre responses (IgG concentrations [specific for GBS-NN and GBS-NN2]) will be listed along with the Day 1 and Day 85 results obtained from the MVX0002 study. Antibody response data will be summarised descriptively using number dosed (N), geometric mean and 95% confidence interval (CI) for the geometric mean, , minimum, median, maximum and interquartile range (IQR), by study (MVX0003, MVX0002) and dose level received in the MVX0002 study (placebo/vaccine naïve, 25ug, 50ug) and active doses pooled. Individual and geometric mean plots of antibody concentrations will also be produced by study and dose level received in the MVX0002 study.

In order to explore the decline in IgG antibodies since the previous study, a statistical comparison of the GBS-NN and GBS-NN2 antibody concentrations on Day 1 of the MVX0003 study and Day 85 of the MVX0002 study will be performed for each of the corresponding MVX0002 dose levels. Following logarithmic transformation, antibody concentrations will be subjected to a mixed effect analysis of variance (ANOVA), with study as a fixed effect and participant as a random effect. Point estimates and 95% confidence interval will be constructed for the contrasts between Day 1 (MVX0003) and Day 85 (MVX0002). The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric least squares means (LSMeans) and corresponding 95% confidence intervals for each MVX0002 dose level and active doses pooled.

A similar ANOVA will also be performed in order to compare the Day 85 GBS-NN and GBS-NN2 antibody concentrations for the MVX0003 study to those obtained for the MVX0002 study, for each of the corresponding MVX0002 dose levels.

Additionally, the GBS-NN and GBS-NN2 antibody concentrations observed on Day 85 of the MVX0003 study will be compared between participants who received 25ug GBS-NN/GBS-NN2 in the previous study and vaccine-naïve participants and between participants who received 50ug GBS-NN/GBS-NN2 in the previous study and vaccine-naïve participants. Following logarithmic transformation, Day 85 antibody concentrations will be subjected to ANOVA, with dose level as a fixed effect. Point estimates and 95% confidence intervals will be constructed for the contrasts between the dose levels. The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric LSMeans and corresponding 95% confidence intervals.

The fold-increase in antibody concentrations specific for GBS-NN and GBS-NN2 will be derived between:

- Day 1 and Day 85 for both the MVX0002 and MVX0003 studies, for each of the corresponding MVX0002 dose levels and all active vaccinees.
- Day 1 of the MVX0003 study and Day 85 of the MVX0002 study, for each of the corresponding MVX0002 dose levels and all active vaccinees.
- Day 85 of the MVX0002 study and Day 85 of the of the current MVX0003 study, for each of the corresponding MVX0002 dose levels and all active vaccinees.

Fold-increases will be listed and descriptive statistics (N, n, arithmetic mean, SD, geometric mean and corresponding 95% CI, minimum, median and maximum and IQR) will be tabulated by study and MVX0002 dose level and all active vaccinees.

In addition, the proportion of participants with concentrations above the pre-determined thresholds of 1, 2, 4 and 8 µg/mL at Day 85 will be presented by study and MVX0002 dose level and all active vaccinees.

Additional Exploratory Pharmacodynamics:

- [redacted].
- [redacted].

DURATION OF STUDY:	Approximately 30 weeks for each individual (from the Screening to post-study follow-up).

4 TABLE OF CONTENTS

TABLES

5 ABBREVIATIONS USED IN THE PROTOCOL TEXT

- ABPI Association of the British Pharmaceutical Industry
- AE(s) adverse event(s)
- ALP alkaline phosphatase
- ALT alanine transaminase
- ANOVA analysis of variance
- AST aspartate transaminase
- BIA BioIndustry Association
- BMI body mass index
- bpm beat(s) per minute
- CCRA Clinical Contract Research Association
- CI confidence interval
- Cl chloride
- COVID-19 Coronavirus 2019
- CRP c-reactive protein
- DoH Department of Health
- EC European Commission
- eCRF electronic case report form
- ECG electrocardiogram
- EDTA ethylenediaminetetraacetic acid
- EOD early onset disease
- eTMF electronic Trial Master File
- FSH Follicle Stimulating Hormone
- GBS Group B streptococcus
- GCP Good Clinical Practice
- GDPR General Data Protection Regulation
- GGT gamma glutamyltransferase
- GMP Good Manufacturing Practice
- h hour(s)
- HBsAg hepatitis B surface antigen
- HCT haematocrit
- HCV Ab hepatitis C virus antibody
- HIV human immunodeficiency virus
- HRA Health Research Authority
- HRT Hormone Replacement Therapy
- IAP intrapartum antibiotic prophylaxis
- IB Investigator's Brochure
- ICF informed consent form
- ICH International Council on Harmonisation
- IG Immunogenicity set
- [redacted]
- [redacted]
- IgG Immunoglobulin G
- IMP investigational medicinal product(s)
- IQR interquartile range
- ISF Investigator site file
- Kg Kilogram
- LDH lactate dehydrogenase
- LOH Late Onset Disease
- LSMeans Least Squares Means
- Ltd Limited
- m meter(s)
- MedDRA Medical Dictionary for Regulatory Activities
- MHRA Medicines and Healthcare products Regulatory Agency
- Mg milligram(s)
- Min minute(s)
- mL millilitre(s)
- Mm millimolar(s)
- mmHg millimetre(s) of mercury
- N number dosed
- n number of observations
- Na sodium
- NRES National Research Ethics Committee
- OPKA Opsonophagocytic Killing Assay
- OTC over-the-counter
- [redacted]
- PCH Prince Charles Hospital
- PCP phencyclidine

- PCR polymerase chain reaction
- PD pharmacodynamic
- PK pharmacokinetic
- PP Per Protocol Set
- PPE Personal Protective Equipment
- QP Qualified Person
- REC Research Ethics Committee
- RT-PCR reverse transcription polymerase chain reaction
- s second(s)
- SAE serious adverse event
- SAF safety set
- SAP statistical analysis plan
- SAR serious adverse reaction
- SAS statistical analysis software by SAS Institute Inc., USA
- SD standard deviation
- SDPE Symptom-Directed Physical Examination
- SmPC Summary of Product Characteristics
- SOC system organ class
- SOP standard operating procedure(s)
- SUSAR suspected unexpected serious adverse reaction
- TEAE Treatment Emergent Adverse Event
- UK United Kingdom
- USA United States of America
- µg microgram

6 ETHICS

6.1 Research Ethics Committee or Institutional Review Board

This study protocol will be submitted to the Research Ethics Committee (REC) for review and provision of a favourable opinion. The favourable opinion of the REC must be obtained before commencement of any study procedures.

The favourable opinion is conditional upon the Sponsor registering the clinical trial in a publicly accessible database, within 6 weeks of the first participant recruited or following confirmation of an appropriate Health Research Authority (HRA) deferral.

All substantial protocol amendments must receive favourable opinion from the REC responsible for the study. Non-substantial amendments will not require prior favourable opinion by the REC.

If the study is stopped due to adverse events (AEs) it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g., completed) will be reported to the REC responsible for the study within 90 days of completion of the last participant's final study procedures. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 days of the decision to stop the study.

A summary of the clinical study report will be submitted to the REC responsible for the study within 1 year of completion of the last participant's final study procedures.

The REC will be informed that Simbec-Orion is a commercial organisation and that the study is funded by MinervaX. The participants who take part in the clinical study will be paid for their inconvenience and have been informed that there will be no benefits gained by their participation. All potential conflicts of interest will be declared by the Investigators.

6.2 Ethical Conduct of the Study

The Principal Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (Brazil 2013). It will comply with International Council on Harmonisation (ICH) Good Clinical Practice (GCP)[1] and applicable regulatory requirements.

6.3 Participant Information and Consent

Potential participants who volunteer for participation in the study will be informed of the aims, methods, anticipated benefits and potential hazards of the study and any possible discomfort it may entail. Information will be given in both oral and written form and in the manner deemed appropriate by the Clinical Unit standard operating procedures (SOPs). Each participant will also be informed of his/her right to withdraw from the study at any time, for any reason.

A written explanation (participant information sheet) and informed consent form (ICF) will be provided, and the participant will be allowed sufficient time to consider the study information. Prior to signing the ICF, the participant will be given an opportunity to discuss any issues concerning the study with an Investigator who has suitable knowledge of the study and will have all questions answered openly and honestly.

If the participant is willing to participate in the study, the ICF form will be signed and personally dated by the participant and the person taking consent. The participant will receive a copy of the ICF form together with the participant information sheet and the original signed ICF will be retained with the study records at the Investigator site. In addition, the actions and completion of the consenting process will be recorded in the participant's medical record (*i.e.*, source document).

7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study will be performed at a single site, Simbec-Orion Clinical Pharmacology Unit. The overall responsibility for the study will rest with the Principal Investigator, Dr Helen Philpott. The Project Manager will act on behalf of the Principal Investigator to ensure the smooth and efficient running of all aspects of the study.

7.1 Study Personnel

Contract Research Organisation: Simbec-Orion

Principal Investigator:	Dr Helen Philpott
Project Manager (Main Contact):	[redacted]
Project Manager Deputy:	[redacted]
Pharmacokinetics (PK):	N/A
Statistics:	Simbec-Orion Biometrics
Data Management:	[redacted]
Laboratory Services:	[redacted]
IMP Management:	[redacted]
Medical Monitoring:	[redacted]

The Principal Investigator will delegate study-related activities according to staff responsibilities and job descriptions. This will be documented in a study-specific delegation of responsibilities form.

Sponsor: MinervaX ApS

Project Manager (Main Contact):	[redacted]
Sponsor's Responsible Physician:	Dr Geoff Kitson
Monitor:	[redacted] (Ascot Research Consulting Ltd.)
Pharmacovigilance (PV):	Diamond PV Services Ltd

7.2 Indemnity Arrangements

The Sponsor and Simbec-Orion carry insurance to pay compensation for injury, accident, ill health or death caused by participation in this study without regard to proof of negligence in accordance with the insurance and compensation in the event of injury in Phase I clinical trials 2012, guidance issued by the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) in consultation with the Department of Health (DoH) and the National Research Ethics Service (NRES).

8 INTRODUCTION

8.1 Background

Group B streptococcus (GBS) has now emerged as the leading cause of neonatal sepsis and is also increasingly recognised as an important cause of disease in adults, especially in the elderly and those with underlying disease[2, 3]. GBS is responsible for 50% of life-threatening infections in new-borns, leading to severe morbidity and life-long disabilities.

GBS neonatal infections are associated with high morbidity and mortality and constitute a major public health problem affecting 0.5 to 3 new-borns per 1000 live births[4]. In the United Kingdom (UK), national surveillance during 2000-2001 identified a total of 568 cases: an incidence of 0.72 per 1000 live births, showing regional variation with 0.42 per 1000 live births in Scotland and 0.9 in Northern Ireland. GBS neonatal infections have been reported in and across Europe, United States of America (USA), Australasia, South Africa, Kenya and Malawi confirming the global nature of the disease.

GBS related neonatal morbidity can be classified into early onset disease (EOD); occurring 1 to 6 days after birth), and late onset disease (LOD); occurring 7 to 89 days after birth). EOD accounts for about 60 to 70% of GBS related neonatal morbidity as a result of vertical transmission of GBS from mother to infant at or around the time of delivery. In over 90% of cases, clinical features of sepsis and pneumonia occur within 12 to 24 hours (h)[5, 6]. In contrast, LOD, which occurs 7 to 89 days post-delivery, and is acquired perinatally, nosocomially or from community sources, presenting with meningitis in up to 30% of cases[7].There is also an association with GBS urinary tract infection in the mother during pregnancy and the occurrence of chorioamnionitis, and premature labour[8, 9].

Introduction of intrapartum antibiotic prophylaxis (IAP) in the year 2000 in birthing women, who are at risk of transmitting GBS to the infant during childbirth due to vaginal/rectal colonisation with GBS or other known risk factors, has reduced the incidences of EOD by up to 80% in countries, like the USA, where universal antenatal screening programs for GBS colonisation during pregnancy have been implemented. Other countries rely on risk assessment based on the factors outlined above, rather than universal screening for GBS colonisation. On average, GBS screening (or risk-assessment) results in some 20 to 50% of birthing women receiving IAP, depending on region.

Despite this widespread use of IAP, EOD has not been reduced by more than 80% at the most, and still affects some 4,500 new-born babies annually in Europe and the USA combined; and the incidences have recently been on the rise again[10]. The failure of IAP to fully eradicate EOD relates primarily to lack of adherence to protocol, poor implementation of protocols, premature delivery, and childbirth lasting less than the 4 h required for IAP to be fully effective.

Importantly, the serious LOD infections (> 50% meningitis) have remained unaffected by IAP, at 3,000 cases annually, due to the fact that nosocomial infections are unaffected by IAP during childbirth. Also, IAP has had no effect on the incidences of GBS induced stillbirths (900) and premature deliveries (7,000), which occur prior to administration of IAP.

In addition to the inability of IAP to completely eradicate EOD and in anyway prevent GBS-induced LOD, stillbirth and preterm labour, the widespread use of antibiotic prophylaxis in GBS prevention has resulted in the emergence of antibiotic resistance in GBS. Penicillin remains the preferred antibiotic prophylaxis, but clinical isolates with reduced sensitivity to

penicillin due to mutations in penicillin-binding proteins have emerged over recent years[111]. The alarming finding is that the emerging patterns of mutations are identical to those observed in *S. pneumoniae* prior to the breakthrough of widespread true penicillin resistance in that pathogen[122, 13]. Full breakthrough of penicillin resistance in GBS will lead to a dramatic increase in the incidences of EOD, potentially returning the world to pre-IAP levels, as well as creating a serious problem when having to treat such infections. IAP has also led to an increase in neonatal infections with antibiotic resistant strains of other bacteria such as *E. coli*.

8.2 Rationale for Study

A large medical need exists for the development of an effective alternative to IAP for the prevention of neonatal GBS infections, as outlined above, and a maternal vaccine would be the appropriate solution.

Immunisation of pregnant women during the latter part of pregnancy, leading to passive immunisation of the unborn child through trans-placental transfer of protective GBS-specific antibodies, would be beneficial. Such antibodies will likely persist for 3-6 months after birth and potentially protect the foetus in-utero, against GBS induced still birth and premature delivery; and the new born baby against both EOD and LOD. A vaccine therefore seems the obvious choice for an alternative to IAP[14, 15, 16].

A number of GBS serotypes can be distinguished based on their type-specific capsular polysaccharides (CPS). This capsule represents a major virulence factor, which helps bacterial invasion by interfering with phagocytic clearance except in the presence of type specific opsonophagocytic antibodies[177, 188]. To date, 10 antigenically unique GBS serotypes have been identified (Ia, Ib, II-IX). Of these serotypes Ia, III and V are the most prevalent in EOD with type III accounting for 36% of EOD and 71% of LOD, and together, serotypes Ia, Ib, II, III and V cover approximately 95% of all isolates.

Spontaneous colonisation of women with GBS is the likely explanation for the existence of naturally occurring antibodies against several GBS antigens in pregnant women. Interestingly, the presence of high concentrations of anti-CPS antibodies in pregnant women has been found to correlate with protection of their off-spring against invasive GBS disease, indicating that vaccine-induced maternal anti-CPS antibodies would indeed be protective[19, 2020, 21].

MinervaX has developed a novel GBS vaccine candidate, GBS-NN, based on the N-terminals of the Rib, AlpC, Alp1 and Alp2/3 surface proteins of GBS. Alp 1 and Alp2/3; (Alp2 and Alp3 have identical N-terminal domains. These N terminal proteins are found on most isolates of serotypes Ia, Ib, II, III, IV, V, VI, VII and VIII, and antibodies directed against the vaccine proteins were found to recognize 80-100% of 154 clinical isolates of serotypes Ia, Ib, II, III and V tested for antibody binding. Naturally occurring antibodies against the full --length Rib and AlpC proteins are found in pregnant women, probably due to exposure to GBS from colonisation, and such antibodies are efficiently transferred to their babies in-utero. Antibodies to Rib and AlpC elicit protective immunity in animal models when administered with the standard adjuvant alum[222].

The GBS-NN/NN2 vaccine contains two fusion proteins – GBS-NN contains the Rib and AlpC proteins and GBS-NN2 contains the Alp1, Alp2 N-terminal proteins Hence, of the four different members of the targeted surface proteins that are found on different GBS bacteria, two are represented in GBS-NN and t two in GBS-NN2.

The clinical use of the GBS-NN/NN2 vaccine will be to protect foetuses and new-born babies from invasive GBS disease. It is anticipated that women will receive an initial course of two doses during their first pregnancy, in which GBS-NN/NN2 is administered. It is not anticipated that this course will protect babies in subsequent pregnancies and a booster dose will be required.

The purpose of this study is to investigate the safety and the immune response induced by a single booster injection in women previously vaccinated with GBS-NN/NN2. The time interval of 1 to 5 years since the primary course is to match a relatively normal interval between children. The study will also compare the safety, tolerability and immune responses between previously vaccinated women, from the MVX0002 study, and those women from the MVX0002 study who received placebo and not the active GBS-NN/NN2 vaccine or new participants who considered vaccine naïve and did not participate in the MVX0002 study (for whom the dose of GBS-NN/NN2 in this study will be considered a first dose). The rationale for the inclusion of such participants is as follows:

- To provide a comparison in safety/tolerability and immune response data between individuals who have received a booster dose of the vaccine versus a single dose administration in previously vaccine naïve individuals.
- To add to the growing body of safety and immunogenicity data generated for the GBS-NN/NN2 vaccine following a single dose administration.
- To evaluate the safety/tolerability and immune response following a single dose administration in comparison with the data generated in the MVX0002 study (based on 2 doses of GBS-NN/NN2 vaccine on Day 1 and Day 29).

8.3 Summary of Non-Clinical Data

Mice have been dosed with GBS-NN with and without alum (Alhydrogel®) at doses ranging from 2 µg to 64 µg using dose interval factors of 2 or 4. Immune responses were elicited at all doses, with the antibody responses at doses of 4 µg to 64 µg in the presence of Alhydrogel® being indistinguishable from each other and showing a trend towards being higher than responses to 2 µg (KWS study MNV008-4-AMI). The addition of Alhydrogel® reduced the time taken for the peak immune response to be achieved, increased the magnitude of the immune response and increased the number of responders.

The local and systemic toxicity studies with GBS-NN/NN2 in rabbits and rats, respectively, did not identify any unexpected findings. The rats received four doses of 100 µg of GBS-NN and 100 µg of GBS-NN2; the doses were administered as two 0.1 mL (50 µg) injections into the right thigh (GBS-NN) and two 0.1 mL (50 µg) injections into the left thigh (GBS-NN2). The rabbits received 4 doses over 28 days of 125 µg of the GBS-NN and 125 µg of GBS-NN2 administered as two separate injections or as a single injection of both proteins mixed together.

The findings of the studies were in-line with the findings GBS-NN alone and the changes seen in the animals were considered to be the pharmacological responses to the vaccine inducing an immune response. Previous studies with GBS-NN alone identified small but statistically significant differences between treated and untreated groups in the red blood cell-related parameters: lower red blood cell count (statistically significant in males, tendency in females); lower haemoglobin (both in males and in females) and lower haematocrit (HCT; statistically significant in males, tendency in the females) in animals treated with GBS-NN vaccine. The

relevance of these findings was unknown but have not been seen in the GBS-NN/NN2 study. Changes in differential leucocyte count, were seen and were regarded as part of the intended pharmacological effect.

Overall, the data indicate that it was appropriate to continue development and administer the GBS-NN/NN2 vaccine to healthy participants.

Reproductive toxicology studies have been completed, in rats GBS-NN/NN2 administered on Days 3, 10 and 18 of gestation was well tolerated and did not adversely affect embryo-foetal development or survival. The treatment of New Zealand white female rabbits with adjuvant or GBS-NN/NN2, on 28, 14 and 7 days before mating and then on Days 3, 13 and 24 of gestation was well tolerated by the females. Effects were restricted to oedema at some injection sites of the females receiving GBS-NN/NN2 following intramuscular administration during the pre-mating or gestation phase. Neither the adjuvant or GBS-NN/NN2 adversely affected female fertility, embryo-foetal development or survival.

Immunogenicity studies with GBS-NN/NN2 have been undertaken in mice (MVX006). Immunisation with either GBS-NN or GBS-NN2 induced significant cross-reactivity with the heterologous antigen. Primary immunisation with the combination of GBS-NN and GBS-NN2 gave similar responses to all four domains and the responses to homologous antigens were equivalent to those induced by immunising with the single molecules.

8.4 Summary of Clinical Data

Study MVX13211 with GBS-NN alone, has shown that GBS-NN was well tolerated in healthy female participants. The study concluded that GBS-NN had an appropriate safety profile for a vaccine with the primary adverse reaction of pain at injection site being mild and reported at an incidence comparable to other intramuscularly administered vaccines that contain Alhydrogel®. Healthy participants developed high concentrations of antibodies against the N terminal proteins AlphaC and Rib and these antibodies are functional in opsonophagocytic killing assays (OPKA). The antibodies are primarily IgG1, which is actively transported across the placenta and therefore, if the antibodies are protective, it is anticipated that the foetus will be passively immunized from the mother.

The first clinical trial with GBS-NN, in healthy non-pregnant women, has shown the Alp-proteins in the vaccine to be highly immunogenic when 2 doses of 50 µg or one or two doses of 100 µg were administered with Alhydrogel®. Geometric mean antibody concentrations were: 2 doses of 50 µg 16.9 µg/mL; 2 doses of 100 µg 15.5 µg/mL; 1 dose of 100 µg 3.0 µg/mL. More than 95% of evaluable participants seroconverted in each of the three dosing groups. However, samples from this trial were analysed in OPK assays and these studies identified the need for the additional antigens, Alp1, Alp2 and Alp3 to be included in a vaccine to broaden the coverage of the vaccine and resulted in the development of GBS-NN/NN2.

Study MVX0002 was a Phase I, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of two doses of group B streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in 60 healthy female participants aged 18 to 40.

The 25 and 50 µg doses of GBS-NN/NN2 were considered to have an acceptable safety profile for a vaccine and to be well tolerated up to 12 weeks (Day 85) post-dose with a favourable safety profile up to 6 months (Day 210) post-dose.

The two vaccine doses induced an immune response in healthy female participants, as reflected by a significant fold increase in IgG (specific for GBS-NN and GBS-NN2) when compared to placebo and a seroconversion rate (> 4-fold increase) of 95.8 – 100% for GBS-NN and GBS-NN2. There was no significant difference in fold increase observed between 25 and 50 µg GBS-NN/NN2 although there was a trend towards a higher fold increase for GBS-NN2 at the 50 µg dose level. Although the immune responses in participants who received the 50 µg dose compared to those who received the 25µg dose were not significantly different, there were trends in all measures (absolute IgG concentrations, fold increases and proportions achieving higher thresholds, functional activity in OPKA against RibN proteins) indicating a more robust immune response to the higher dose. This, combined with the fact that the higher dose was equally well tolerated, indicates that the 50 µg dose is appropriate for further development.

The 50 µg dose is now being administered in a phase 2 study in South Africa in pregnant women.

Further details of the non-clinical studies and a summary of the known and potential risks and benefits to human participants of GBS-NN/NN2 can be found in the Investigator's Brochure (IB)[23].

The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s), as indicated within Section 6.2.5 of the ICH GCP E6 (R2) guidelines[24].

8.5 Risk-Benefit Assessment

8.5.1 Risks

From the data gathered to date; administration of GBS-NN/NN2 has been associated with mild, self-limiting pain at the injection site. No systemic risks have been identified. There have been no reports of significant or persistent lesions at the injection site. The incidence of miscarriage, post-vaccine exposure, is in line with the incidence seen in the general population and was comparable between the active and placebo groups with no dose relationship[23]. To date 48 pregnant women have received their first dose and 31 their second dose, in South Africa (Study MVX0005) and GBS-NN/NN2 has been well tolerated. Fourteen healthy babies have been born to date.

8.5.2 Benefits

No clear benefits have been identified as efficacy has not been assessed. It is apparent that GBS-NN/NN2 induces an immune response but it is not known if the immune response is protective, as this has not been studied. The immune response generated has been shown to induce IgG1 antibodies; it is the IgG1 antibodies that are actively transported across the placenta. An analysis of the opsonophagocytic activity of the antibodies generated against GBS-NN and GBS-NN/NN2 has shown that the antibodies have functional activity. The antibodies to the GBS-NN vaccine have also demonstrated an ability to completely block the epithelial invasion by GBS, at antibody concentrations below 50 ng/mL. The addition of the N-terminal proteins for Alp1 and Alp2/3 has induced a broader immune response with no additional toxicity[23].

8.6 Reference Safety Information

Based on the current human exposure to GBS-NN/NN2, there are no expected serious AEs and all suspected unexpected serious adverse reactions will be reported[233].

8.7 Coronavirus Disease 2019 (COVID-19) Risk/Benefit Assessment

This study is to be conducted in healthy adult participants who are deemed not to be at high risk of COVID-19 as per the latest NHS Guidance (https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/whos-at-higher-risk-from-coronavirus/).

The safety of participants is the primary concern. This study is to be conducted at the Simbec-Orion Clinical Pharmacology Unit which is a Phase I accredited unit with extensive experience in conducting Phase I trials of similar design. Simbec-Orion prioritise the health and wellbeing of their clinical trial participants and, as such, have implemented a number of COVID-19 policies and risk mitigating actions. Prior to attendance at site, participants will be contacted to ensure they are not displaying any COVID-19 symptoms; Site COVID-19 policies will be explained to them at this time. Where appropriate, Perspex screens are in place and appropriate social distancing is enforced. Where this is not possible, appropriate Personal Protective Equipment (PPE) will be worn.

Simbec-Orion Clinical Pharmacology unit is a dedicated trial facility and, as such, staffing levels will not be affected by the potential burden presented by COVID-19 to other medical facilities. All employees present at the clinical site are aware of the COVID-19 specific working requirements and will work to the relevant 'Working Safely' Policy.

Medicines and Healthcare products Regulatory Agency (MHRA) Phase I Accreditation requirement No. 3 details the requirement for an agreement with a local hospital for supporting emergencies arising from the clinical trials performed by Simbec-Orion. This agreement is in place with Cwm Taf University Health Board and Prince Charles Hospital (PCH) for this purpose. Cwm Taf University Health Board and PCH have confirmed capacity to support any acute serious AEs (SAEs) during the COVID-19 pandemic (details contained within the latest current version of the Simbec-Orion Clinical General Risk Assessment).

The Investigational Medicinal Product (IMP) is not an immunosuppressant. There is no scientific evidence that GBS-NN/NN2 vaccine increases a participant's susceptibility to COVID-19 or will exacerbate a participant's condition should they contract COVID-19. In addition, all participants will be under the medical supervision of the Principal Investigator while they are onsite at Simbec.

Both the Study and Site Risk Assessments will be continually monitored and updated throughout the trial and it is currently deemed acceptable to conduct the trial without it impacting or being impacted by the COVID-19 pandemic.

In addition, the sponsor has conducted a risk assessment in consideration of the ongoing COVID-19 vaccine deployment programme including assessment of the potential risks associated with concomitant vaccination whilst participating in this trial.

The sponsor has determined that the outcome of the risk assessment undertaken in conjunction with the study team is that participants will be permitted to have their COVID vaccination whilst in the study and is considered as a concomitant medication with no interaction. Administration of the COVID vaccine and the GBS-NN/NN2 vaccine will be separated by at least 7 days.

Participants will be informed that they are to notify the Simbec-Orion team if they are invited to receive a COVID-19 vaccine at any point during the study so that this may be documented accordingly and the timing of the GBS-NN/NN2 vaccine can be adjusted to allow participants to have their COVID vaccination as it is scheduled.

Concomitant administration of GBS-NN/NN2 during an ongoing round of vaccination will not, to the best extent of available knowledge, compromise the efficacy of any current approved COVID-19 vaccine or otherwise induce or exacerbate any effects of current approved COVID-19 vaccines or have any known undue interactions. The study team will continue to review and monitor any update in terms of COVID-19 vaccine interaction with medications within the relevant therapeutic class for GBS-NN/NN2. This will include an assessment of any further COVID-19 vaccines which receive approval for use during the course of the study.

9 STUDY OBJECTIVES

9.1 Primary Study Objective

- To evaluate the safety over 12 weeks of a single booster dose of the GBS vaccine GBS-NN/NN2, administered 1 to 5 years after completion of the initial primary vaccination course and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants).

9.2 Secondary Study Objectives

- Safety Objectives: To evaluate the long-term safety profile of the GBS-NN/NN2 vaccine 6 months following the booster dose in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.
- Immunological Objectives:
    - To evaluate the IgG antibody responses, specific to GBS-NN and GBS-NN2 fusion proteins, on Day 1 and Day 85 in previously vaccinated healthy female participants and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.
    - To evaluate the IgG antibody responses, specific to AlpCN, RibN, Alp1N and Alp2-3N, on days 1, 8, 29, 57, 85 and 183, in previously vaccinated healthy female participants and in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants) who have received a single first dose of GBS-NN/NN2 vaccine.

9.3 Exploratory Study Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is an open label vaccine booster follow-up study. Participants who have received a primary course of GBS-NN/NN2 or placebo in Study MVX0002 will be invited to return to receive a booster dose (or first dose in the case of placebo or vaccine naïve participants) 1 to 5 years after the completion of the primary course of vaccination. All participants will receive a single dose of GBS-NN/NN2 containing 50µg of each fusion protein.

A minimum of 30 and a maximum of 40 female participants will be recruited, comprised of between 20 and 30 participants who had received previous vaccination with GBS-NN/NN2 in the MVX0002 study and up to 10 participants who had received placebo in the MVX0002 study. If an insufficient number (<5) of previous placebo recipient participants return to this study, vaccine naïve participants will be recruited.

The study will include 7 visits (Visit 1: Screening Period, Visits 2-6: Treatment Period and Visit 7: Post-study Follow-up).

The clinical phase is anticipated to take place between June/July 2021 and January/February 2022. The conclusion of the study is defined as last participant last visit.

The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology under full medical and nursing supervision.

A schedule of all study assessments is provided in Table 10.7.1.

10.2 General Stopping Criteria

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Principal Investigator (or deputy) and the Sponsor. A written document signed by the Principal Investigator (or deputy) and Sponsor will be produced ratifying the decision.

If any of the following stopping criteria are met, the study will be temporarily halted:

- a ‘serious’ adverse reaction (i.e. a serious adverse event considered at least possibly related to the IMP administration) in one subject.
- ‘severe’ adverse reactions (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration) in two subjects, independent of within or not within the same system-organ-class.

If the study is temporarily halted for any reason including the circumstance where any of the above stopping criteria are fulfilled, the study will only proceed and restart once an appropriate substantial amendment has been submitted and receives regulatory approval from the MHRA and approval from the REC associated with the study. Individual participants may also be withdrawn for any of the reasons outlined in Section 10.5.4.

10.3 Discussion of Study design, including the choice of Control Groups

A large medical need exists for the development of an effective alternative to IAP for the prevention of neonatal GBS infections, as outlined above and a maternal vaccine would be the appropriate solution.

MinervaX has developed a novel GBS vaccine candidate, GBS-NN/NN2, based on the N-terminals of the surface proteins of GBS.

The clinical trials with GBS-NN (Study MVX13211) and with GBS-NN/NN2 (Study MVX0002) in healthy non-pregnant women, have shown the potential vaccine to be highly immunogenic well tolerated with a good safety profile.

This study is a follow-on study to assess the safety and immunogenicity of a booster dose of GBS-NN/NN2 vaccine, 1 to 5 years after participants in study MVX0002 have completed the primary vaccination course, in comparison to vaccine naïve participants (either placebo recipients from study MVX0002 or new vaccine naïve participants). The rationale for the inclusion of such participants is as follows:

- To provide a comparison in safety/tolerability and immune response data between individuals who have received a booster dose of the vaccine versus a single dose administration in previously vaccine naïve individuals.
- To add to the growing body of safety and immunogenicity data generated for the GBS-NN/NN2 vaccine following a single dose administration.
- To evaluate the safety/tolerability and immune response following a single dose administration in comparison with the data generated in the MVX0002 study (based on 2 doses of GBS-NN/NN2 vaccine on Day 1 and Day 29).

10.4 Selection of Study Population

All women who have participated in Study MVX0002 with GBS-NN/NN2 will be re-contacted and invited to participate in this study. It is intended to recruit 20 to 30 women who have received a primary course of vaccination with GBS-NN/NN2 and up to 10 women who received placebo in the MVX0002 study. If insufficient (<5) participants who received placebo in Study MVX0002 return to this study, vaccine naïve participants will be recruited.

The following eligibility criteria are designed to select participants for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular participant.

Deviations from inclusion and exclusion criteria are not allowed as deviations have the potential to impact the scientific integrity of the study, regulatory acceptability or participant safety as such deviations constitute a deliberate breach of Regulation 29 of Statutory Instrument (SI) 2004/1031. Therefore, adherence to the criteria as specified in the protocol is essential.

10.4.1 Inclusion Criteria

To be confirmed at Screening:

1. Women who have participated in study MVX0002, with GBS-NN/NN2 vaccine and received active vaccine or placebo (unless it is necessary to recruit vaccine naïve participants to bolster the number of participants who received placebo in MVX0002).
2. Able to voluntarily provide written informed consent to participate in the study.
3. Healthy female participants aged 18-40 years (vaccine naïve participants only).
4. Female participant of childbearing potential willing to use a highly effective method of contraception (in addition to a condom for male partners), if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from the first dose until completion of the Day 85 visit. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. *For the purposes of this study, this definition of a female of childbearing potential applies to all females in the study i.e., those who participated in the MVX0002 study and those who are considered vaccine naïve.*
5. Female participant of non-childbearing potential. *For the purposes of this study, this is defined as the participant being at least 4 months post-surgical sterilisation (including bilateral fallopian tube ligation or bilateral oophorectomy with or without hysterectomy).*
6. Female participant with a negative pregnancy test at Screening and prior to dose.
7. Female participant of menopausal status confirmed by demonstrating at Screening that the serum level of the follicle stimulating hormone (FSH) falls within the respective pathology reference range. In the event a participant's menopausal status has been clearly established (for example, the participant indicates she has been amenorrhoeic for 10 years, confirmed by medical history, etc), but serum FSH levels are not consistent with a postmenopausal status, determination of the participant's eligibility to be included in the study will be at the Investigator's discretion following consultation with the Sponsor.
8. Body mass index (BMI) ≥18 and ≤30 kg/m^2 (vaccine naïve participants only).
9. Participants' weight ≥ 50 kg and ≤ 100 kg at Screening (vaccine naïve participants only).
10. Non-smokers for at least 3 months prior to study vaccine administration.
11. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before dose administration of the IMP.
12. Participants with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion, if on prescribed opiates resulting in a positive test, participants may be eligible at the investigators discretion).

13. No clinically significant abnormalities in vital signs (supine blood pressure/heart rate, respiration rate, tympanic temperature) determined within 28 days before dose of IMP.
14. Participants with a negative COVID-19 test on admission (Day 1 or Day-1 if deemed appropriate by the Principal Investigator (PI)) if required at the time.

To be re-confirmed prior to dose administration:

1. Participants continue to meet all screening inclusion criteria.
2. Participants with a negative urinary drugs of abuse screen (including alcohol) prior to dose administration.
3. Participants with a negative pregnancy test.
4. Participants with a negative COVID-19 test on admission (Day 1) (or Day -1 if deemed appropriate by the PI) if required at the time.

10.4.2 Exclusion Criteria

To be confirmed at Screening:

1. Participants who have an autoimmune disease.
2. Participants who have a current infection or any significant illness at Screening (such participants can be rescreened once the active infection or significant illness has resolved).
3. Participants with history or presence of significant cardiovascular disease, pulmonary, hepatic, gallbladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, autoimmune disease or current infection.
4. Laboratory values at Screening which are deemed by the Investigator to be clinically significantly abnormal.
5. Positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab).
6. Participation in a clinical drug study during the 90 days or 5 half-lives, whichever is longer, preceding the initial dose in this study (such participants can be rescreened once the 90-day or 5 half-lives period has elapsed).
7. Participants with a history of severe allergic reactions after previous vaccination.
8. Participants with a history of hypersensitivity to the IMP or any of the excipients within the IMP or documented allergy to aminoglycosides.
9. Participants who have received any vaccine within 7 days of dosing, or who are planning to receive a vaccine up to 7 days after receiving the GBS-NN/NN2 vaccine.
10. Participants who have received immunosuppressive therapy within the 6 months prior to Screening.
11. Participants with tattoos at the proposed site of vaccine administration.
12. Participants who, in the opinion of the Investigator, are unsuitable for participation in the study.

13. Pregnant or breast feeding.
14. Current or history of drug or alcohol abuse, or a positive urine alcohol test prior to dosing (prescribed opiates are acceptable).
15. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP with the exception of contraceptives and paracetamol (*applies to vaccine naïve participants i.e., those who did not participate in the MVX0002 study and participants from the MVX0002 study (both active and placebo) who have not developed new medical conditions which require the use of chronic medications considered as permitted)*. If participants who participated in the MVX0002 study (either active or placebo recipients) have developed new medical conditions which require the use of chronic medications that do not affect the immune system, the inclusion of such participants will be permitted at the discretion of the Investigator on a case-by-case basis and, only if it is considered that the inclusion within the MVX0003 study will not be detrimental to participant safety.
16. Donation of blood or blood products within 90 days prior to vaccine administration.

To be re-confirmed prior to dose administration:

1. Development of any exclusion criteria since the Screening visit.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since the Screening visit with the exception of contraceptives and paracetamol (*applies to vaccine naïve participants i.e., those who did not participate in the MVX0002 study and participants from the MVX0002 study (both active and placebo) who have not developed new medical conditions which require the use of chronic medications considered as permitted)*.
3. Participation in a clinical study since the Screening visit.
4. Donation of blood or blood products since the Screening visit.

10.5 Additional Advice and Restrictions for Study Population

10.5.1 Contraception

Females of childbearing potential must have had a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to dose.

To prevent pregnancy, female participants of childbearing potential must be willing to use a highly effective method of contraception (in addition to a condom for male partners), if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse was in-line with the preferred and usual lifestyle of the participant [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]) from the first dose until completion of the Day 85 visit.

Highly effective methods of contraception include:

- Combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal and transdermal) associated with inhibition of ovulation,

- Progestogen-only hormonal contraception (oral, injectable and implantable) associated with inhibition of ovulation,
- Intrauterine device (IUD),
- Intrauterine hormone-releasing system (IUS),
- Bilateral tubal occlusion,
- Vasectomised partner (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). In the absence of such documentation, condoms will be required for the male partners. For female participants on the study, the vasectomised male partner should be the sole partner for that participant.

The chosen contraception method(s) must have been followed from the first dose until at least Day 85 of the study.

Participants do not have to use highly effective contraception following the Day 85 visit. Should any participant become pregnant between Day 86 and Day 183, permission will be sought to follow the pregnancy and to obtain data on the outcome of the pregnancy.

10.5.2 Diet and Fluid Restrictions

10.5.2.1 Mealtimes/Fasts

Participants should be fasted 4 hours fast prior to their screening visit. There are no meal restrictions and no fasts required during the clinical conduct of the study.

10.5.2.2 Fluid Intake

There are no fluids restrictions.

10.5.2.3 Alcohol Intake

Consumption of alcoholic beverages within 24 h prior and post dosing and scheduled clinic visits is not allowed.

Any deviation outside this alcohol intake restriction will be assessed on a case-by---case basis at Investigator's discretion (provided the participant's alcohol intake will not impact in the safety aspects and objectives of the study and the participant has a negative alcohol screen prior to dosing).

10.5.2.4 Caffeine

There are no caffeine restrictions during the study.

However, there are no caffeinated drinks available in the Clinical Unit.

10.5.2.5 Poppy and Sesame Seeds

Participants will be advised that they must not eat food containing poppy and/or sesame seeds for 3 days before each visit to the Clinical Unit, as consumption of poppy and/or sesame seeds can lead to a positive opiate result in the drugs of abuse test.

10.5.2.6 Grapefruit Juice and Other Restrictions

There are no restrictions on having food or drink containing grapefruit, cranberry, or Seville oranges.

10.5.3 Other Life-Style Restrictions

Participants are required to abstain from:

- Donation of blood or blood products for 90 days after dose of IMP.
- Use of cosmetics or creams at the site of vaccination that were known to cause irritation, within 24 h prior to dosing and for the duration of the study.
- Excessive exercise or a significant change in usual exercise habit within 7 days prior to dosing and for 7 days post-dosing.

10.5.4 Removal of Participants from Further Assessment

Each participant will be informed of their right to withdraw from the study at any time and for any reason.

An Investigator may withdraw participants from the study at any time for any of the following reasons:

- If a participant experiences a serious or intolerable AE, that prevents them from continuing. Participants will be followed-up for safety and until resolution of the AE unless lost to follow-up.
- If a participant incurs a significant protocol violation which impacts on their safety or the scientific integrity of the study.
- At the request of the Sponsor.
- If it is considered that the participant's health is compromised by remaining in the study or the participant is not sufficiently cooperative.
- If a participant is lost to follow-up.
- Pregnancy before Day 85 (will be discussed with the participant and sponsor to establish continuation of monitoring required).

All cases will be discussed on a case-by-case basis with the sponsor. The decision and the reason for any participant withdrawal will be recorded on the study completion form of the electronic case report form (eCRF).

If a participant is withdrawn or chooses to withdraw from the study for any reason every possible effort will be made to perform the evaluations described for the post-study follow-up (see Table 10.7.1). The data collected from withdrawn participants will be included in the study report.

In the event of any abnormalities considered to be clinically significant, participants will be followed-up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organised if considered necessary.

A minimum of 30 and maximum of 40 female participants are required to complete the study. Participants who withdraw from the study before receiving any IMP will be replaced if suitable reserves are available. Participants who are withdrawn from the study due to significant drug-related AEs will not be replaced. Replacement of all other participants withdrawn from the study after receiving IMP will be decided on a case-by-case basis by the Principal Investigator (or deputy) and Sponsor.

10.6 Investigational Medicinal Product

10.6.1 Identity

The GBS-NN/NN2 vaccine will be supplied as a pre-mixed sterile solution for injection, comprising of 0.35 mg/mL of GBS-NN, 0.35 mg/mL of GBS-NN2 in 7 mM phosphate, 150 mM NaCl pH 7.2. The vial volume is 2.5 mL.

Alhydrogel will be supplied as a sterile suspension for injection containing Alhydrogel 0.5 mL at 1.4 mg/mL Al3+.

Active doses will be assembled by transferring 0.2 mL of GBS(NN+NN2) into a vial of Alhydrogel, inverting gently and then withdrawing 0.5 mL for injection.

The identity of each IMP is detailed in Table 10.6.1.

Table 10.6.1 Identity of Investigational Medicinal Products

Product Name	Strength[1]	Form
Pre-mixed vial containing 0.35 mg/mL each of GBS-NN and GBS-NN2	0.35 mg/mL each of GBS-NN and GBS-NN2	Sterile solution for injection (2.5 mL)
Alhydrogel®	1.4 mg/mL Al3+ ion	Sterile suspension for injection (0.5 mL)

10.6.2 Receipt and Storage

The IMP (pre-mixed vial containing 0.35 mg/mL each of GBS-NN and GBS-NN2) will be supplied by the Sponsor.

The Sponsor must notify the Principal Investigator, or the Project Manager, prior to dispatch of IMP supplies, and of the anticipated date of their arrival. IMP should arrive at the study site at least 7 days before the first dosing day. The Sponsor shall address all supplies to:

The Production Manager

IMP Management
Simbec-Orion
Merthyr Tydfil Industrial Park
Merthyr Tydfil CF48 4DR

Upon receipt, supplies will be dealt with as per Simbec-Orion SOPs. Temperature monitors included with shipments will be downloaded.

On receipt at the Investigator site, IMPs will be stored under quarantine in a segregated, trial specific GMP area. Pre-mixed vial containing 0.35 mg/mL each of GBS-NN and GBS-NN2 will be stored at -20°C. Alhydrogel® will be stored at 2 to 8°C. A Simbec-Orion Qualified

Person (QP) will review the shipping documentation and bulk product QP certification. The supplies will be subsequently removed from quarantine and approved for use.

10.6.3 Assembly and Release

The IMP will be assembled into unit doses by suitably trained Simbec-Orion staff according to Simbec-Orion SOPs.

The IMP will be labelled as specified in Annex 13 (manufacture of IMPs) of the European Commission (EC) guide to Good Manufacturing Practice (GMP)[255].

The finished IMP will be certified by a Simbec-Orion QP and stored in a secure, temperature-controlled GMP area according to Simbec-Orion SOPs.

10.6.4 Administration

The finished IMP (individual subject doses) will be presented in labelled syringes containing 0.5 mL for intramuscular administration with a 24-h expiry.

All participants will receive a 0.5 mL intramuscular injection of 50 µg GBS-NN/NN2 on Day 1.

Administration will be by intramuscular injection, preferably into the deltoid muscle of non-dominant arm. The dominant arm may be used if it is not possible to administer into the non-dominant arm e.g., due to a tattoo.

IMP administration, including the time and site, will be documented in the eCRF.

10.6.5 Return/Destruction

All used IMP containers and unused IMP will be held under quarantine pending return/destruction.

The Sponsor must provide approval for return/destruction of all remaining IMP within 8 weeks study completion. After this period, a charge for storage will be incurred.

All returns will be arranged at the earliest available delivery date. For IMP destruction, the Sponsor will receive the Certificate of Destruction 4 to 6 weeks from the date of removal from site.

10.6.6 Method of Assigning Participants to Treatment Groups

This is an open label study. All participants will receive a single intramuscular injection of GBS-NN/NN2 containing 50 µg of GBS-NN and 50 µg of GBS/NN2.

Participants will be numbered sequentially from 001 (i.e., 001, 002 etc.). Replacement participants will be assigned the same number as the participant they are replacing, however, 100 will be added to the number (i.e., 101 would replace 001 etc.).

10.6.7 Selection of Doses in the Study

The dose selected is based on safety and Pharmacodynamic (PD) data from MVX0002 study.

10.6.8 Timing of Dose for Each Participant

Doses will be administered after all pre-dose assessments have been completed.

10.6.9 Blinding

Not applicable, all participants will receive a single dose of GBS-NN/NN2 containing 50µg of each fusion protein.

10.6.10 Prior and Concomitant Therapy

10.6.10.1 Prior Medication:

Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken within 28 days (or 5 half-lives (whichever is longer)) prior to the first dose of IMP with the exception of contraceptives and paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h). If applicable this will be noted in the participant's eCRF.

The use of prior medication is not permitted for any vaccine naïve participants i.e., those who did not participate in the MVX0002 study or for individuals who participated in the MVX0002 study (both active and placebo) who have not developed new medical conditions which require the use of chronic medications considered as permitted as detailed below.

If participants who participated in the MVX0002 study (either active or placebo recipients) have developed new medical conditions which require the use of chronic medications that do not affect the immune system, the inclusion of such participants will be permitted at the discretion of the Investigator on a case-by-case basis and only if it is considered that the inclusion within the MVX0003 study will not be detrimental to participant safety. Any use of prior medication in this circumstance will be noted in the participant's eCRF.

10.6.10.2 Concomitant Therapy

Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken throughout the duration of the study, with the exception of contraceptives and paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h).

If participants who participated in the MVX0002 study (either active or placebo recipients) are taking chronic medications which are considered permitted by the Investigator i.e., those that do not affect the immune system, the use of this medication concomitantly will be permitted as prescribed and will be noted in the participant's eCRF.

All concomitant medications taken during the study including the daily dosage, duration and reasons for administration will be recorded in the eCRF.

10.6.11Treatment Compliance

The vaccine will be administered by a physician; thus, compliance will be assured. The exact dosing time for each participant will be recorded on the participant's eCRF.

10.7 Efficacy and Safety Variables

10.7.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study assessments is provided in the Study Flow Chart, Table 10.7.1.

Simbec-Orion personnel who have been appropriately trained will carry out study procedures.

Where more than 1 procedure is scheduled for the same time-point, the following order of priority will apply:

1. PD blood sampling: Post-vaccination blood samples collected outside of the defined deviation windows will be recorded as protocol deviations: ± 1 day on Day 8, ± 2 days on Day 29 and Day 57, ± 5 days on Day 85 and ± 7 days on Day 183.
2. Vital signs: Vital sign assessments performed outside of the defined deviation windows will be recorded as protocol deviations: ± 5 minute (min) on Day 1, ± 1 day on Day 8, ± 2 days on Day 29 and Day 57, ± 5 days on Day 85 and ± 7 days on Day 183.

Baseline PD samples and vital sign assessments will be performed within the 1 h before dosing.

Table 10.7.1 Study Flow Chart

	Screening Period	Treatment Period					Safety Follow-Up
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Assessment	Day -28 to Day -1	Day 1	Day 8 (±1day)	Day 29 (±2days)	Day 57 (±2days)	Day 85 (±5days)	Day 183 (±7days)
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Subject number and IMP received in MXV0002 study	X						
Demography	X						
Medical History	X						
Physical Examination[1]	X (Full)	X (Brief & SDPE)	X (Brief)	X (Brief)			X (Brief)
Height, Weight, BMI	X						
Vital Signs[2]	X	X	X	X	X	X	X
12-lead ECG	X						
Urinalysis	X						X
Laboratory Safety Tests (Biochemistry and Haematology)	X		X	X	X		X
Virology (HIV, HBsAg and HCV Ab)	X						
Pregnancy Test	X (Serum)	X (Urine)					X (Urine)
FSH[3]	X						
Urine DOA including alcohol and cotinine tests	X	X					
Review of Participant Eligibility		X					
Administration Investigational vaccine		X					
PD Blood Sample – Antibody Response[4]		X	X	X	X	X	X
Exploratory Blood Sample – [redacted][5]		X	X				
Blood sample for future work[6]				X	X	X	
Assessment of Injection Site[7]		X	X	X	X	X	
AE Check		X					
Concomitant Medication Check	X	X					
COVID-19 [8]		X					
Participant Diary Card Day 1 to Day 7[9]		X					
Participant Diary Card Day 85 to Day 183[10]						X	

Study Flow Chart Footnotes:

1. Physical examination: Full physical examination will be performed at Screening. A brief physical examination will be performed pre-dose on Day 1 and a Symptom-Directed Physical Examination (SDPE) will be performed prior to discharge at 30 min (±5 min) post-dose on Day 1. Brief physical examinations will also be conducted on Day 8, Day 29 and at the safety follow up visit (Day 183). A physical examination may also be conducted at any other time point during the study if clinically indicated.

2. Vital signs (Supine heart rate, blood pressure, tympanic temperature and respiration rate) will be measured at Screening, Day 1 (pre-dose and 30 min (±5 min) post dose), Day 8, Day 29, Day 57, Day 85 and Day 183.
3. For postmenopausal female participants only.
4. PD blood samples (antibody response) will be collected on Day 1 (pre-dose), Day 8, Day 29, Day 57, Day 85, and Day 183. GBS-NN/GBS-NN2 will be analysed on Day 1 and Day 85 only.
5. Exploratory blood samples ([redacted]) will be collected on Day 1 (pre-dose) and Day 8.
6. Blood samples for future validation and calibration work will be collected on Day 29, Day 57, and Day 85.
7. Injection site assessment will be performed at pre-dose and 30 min (±5 min) post dose on Day 1, Day 8, Day 29, Day 57, and Day 85. Photographs may be taken of injection site reactions as required.
8. COVID-19 test to be performed at Visit 2, Day 1 (or at Visit 1, Day -1 as determined by the PI) if required.
9. Participant Diary Cards will be completed by participants at home to record morning and evening temperatures, injection site reactions and general reactions, and any AEs and concomitant medication, from the evening of Day 1 to the evening of Day 7. On return to the clinic on Day 8, any out of range temperatures, reactions, AEs or concomitant medication will be recorded in the eCRF.
10. Participant Diary Cards will be completed by participants at home to record any adverse events and concomitant medication from Day 85 to Day 183. On return to the clinic on Day 183, any AEs or concomitant medication will be recorded in the eCRF.

AE = adverse events, BMI = body mass index, ECG = electrocardiogram, HBsAg = hepatitis B surface antigen, HCV Ab = hepatitis C virus antibody, HIV = human immunodeficiency virus, [redacted], PD = pharmacodynamic

10.7.1.1 Demographic and Background Assessments

Demographic and background assessments will be performed during the study at the time-points specified in Table 10.7.1.

10.7.1.1.1 Demographics

Demographic data: age, year of birth, gender, race, ethnicity, height, weight, and BMI.

Height in metres (to the nearest cm) and weight in kg (to the nearest 0.1 kg) in indoor clothing and without shoes will be measured. BMI = body weight (kg) / [height (m)]^2 will be calculated.

10.7.1.1.2 Medical History and Concurrent Conditions

Relevant medical history and current conditions will be recorded in the eCRF.

10.7.1.1.3 Virology Tests

Virology tests: HBsAg, HCV Ab and HIV test (antibodies to HIV-1 and HIV-2).

Virology tests will be analysed from the same serum sample for biochemistry analyses at Screening by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

10.7.1.1.4 COVID-19 Testing:

A nasopharyngeal and/or oropharyngeal swab will be collected. COVID-19 testing will be routinely performed via lateral flow test or real time polymerase chain reaction (RT-PCR) as deemed appropriate by the Principal Investigator.

10.7.1.1.5 Drugs of Abuse (including Alcohol and Cotinine)

Urine DOA screen (including alcohol and cotinine): Amphetamine, Alcohol, Benzodiazepine, Barbiturates, Cannabis, Cocaine, Cotinine, Methadone, Opiates, phencyclidine (PCP).

A **mid-stream** urine sample will be collected into a universal collection/storage container. At protocol-defined time-points when both urinalysis and drugs of abuse/alcohol screening are required, all urine analyses will be performed from a single approximately 30 mL urine sample.

Urine samples for drugs of abuse (including alcohol and cotinine) will be analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/manual kit(s)/method(s) of analyses.

Assessments of urine sample quality (i.e., urine sample verification/adulteration) will be performed by measuring urine creatinine for urine DOA.

10.7.1.1.6 Pregnancy Test, Menstrual and Obstetric History

Pregnancy tests will be performed on all participants (regardless of postmenopausal or sterilised status). Pregnancy tests will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory. Serum pregnancy tests will be performed using an appropriate analyser/manual kit(s)/method(s) of analysis. Urine pregnancy tests will be performed manually using an appropriate pregnancy test kit/method(s) of analysis.

FSH will only be used to confirm menopausal status on women who have had no menses for 12 months without an alternative medical cause, and who are not using hormonal contraception or hormone replacement therapy (HRT). In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Serum FSH to confirm post-menopausal status will be analysed from the same serum sample for biochemistry analyses at Screening for postmenopausal females only**.** Serum FSH analysis will be performed by Simbec-Orion Laboratory Services using the Roche cobas® c6000 analyser series comprising of the c501 and e601 modules or any other appropriate analyser.

10.7.1.2 Compliance with Inclusion/Exclusion Criteria

An Investigator will assess all participants against the study inclusion and exclusion criteria at Screening. Compliance will be re-confirmed prior to dosing on Day 1.

10.7.1.3 Efficacy Assessments

Not applicable.

10.7.1.4 Safety Assessments

The following safety assessments will be performed at the time-points specified in Table 10.7.1

10.7.1.4.1 Adverse Events

AEs and serious adverse events (SAEs) that occurred during the study along with their severity and relationship to study drug will be reported.

An AE is defined as per Statutory Instrument 2004 No. 1031:

Any untoward medical occurrence[1] in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.[2]

Notes:

[1] Whether subjective complaint or objective finding.

[2] An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

An unexpected adverse reaction is defined as:

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product of summary of product characteristics (SmPC) for an authorised product).

AEs will be monitored throughout the study from the signature of participant informed consent through to the post-study follow-up visit. All AEs will be recorded, whether considered minor or serious, drug-related, or not.

All abnormal laboratory findings considered to be clinically significant will be recorded as AEs.

Any out of range temperatures, injection site reactions and/or general reactions recorded in the Patient Diary Card for Day 1-Day 7 will be recorded as AEs.

Recording of Adverse Events

All of the following details will be recorded in the participant's eCRF for each AE:

- Full description of AE.
- Date and time of onset.
- Ongoing (Yes/No).
- End Date and time.
- Severity of event to be assessed by an Investigator in accordance with the definitions below.
- Serious Adverse Event (Yes/No) and seriousness criteria (if applicable)
- Relationship to IMP to be assessed by an Investigator in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

Grades of Adverse Event Severity

The following grades will be used by an Investigator to describe the severity of AEs.

The following are the only grades, which will be used to describe AE severity. Only 1 severity grade will be used for each AE (e.g., mild - moderate is not acceptable).

SEVERITY OF THE AE	DEFINITION
Mild	The AE does not interfere with the participant's daily routines. It causes no more than slight discomfort or mild objective change in any of the safety parameters assessed during the study as determined by the Investigator.
Moderate	The AE interferes with some aspects of the participant's daily routines or moderate objective change in any of the safety parameters assessed during the study as determined by the Investigator.
Severe	The AE causes inability to carry out the participant's daily routine or severe objective change in any of the safety parameters assessed during the study as determined by the Investigator.

Definitions of Adverse Event Causality

The following definitions will be used by an Investigator to describe the relationship between an AE and the IMP.

The following are the only definitions which will be used to describe the relationship between AEs and the IMP. Only 1 relationship definition will be used for each AE.

RELATIONSHIP TO IMP	DEFINITION
Reasonable possibility	• There is a reasonable possibility of the event being related to the IMP. This might be temporal or due to a physiological or pharmacodynamic process
No reasonable possibility	• No reasonable possibility of the event being related to the IMP, the IMP may not have been administered, no temporal relationship, and no known or understood physiological or pharmacological mechanism for the event to be related

Serious Adverse Events

"SAE", "serious adverse reaction" or "unexpected serious adverse reaction" is defined in Statutory Instrument 2004 No. 1031 as any AE, adverse reaction or unexpected adverse reaction, respectively, that

a. results in death,

Note: Death is an outcome (of an AE, of progressive disease, etc.) and not an AE in itself.

b. is life-threatening,

A life-threatening event places the patient at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c. requires hospitalisation or prolongation of existing inpatients' hospitalisation,

"In-patient hospitalisation" means that the patient has been formally admitted to a hospital for medical reasons, for any length of time. It does not include presentation to or care within an emergency department.

Complications that occur during hospitalisations are AEs. If a complication prolongs hospitalisation, it is an SAE.

d. results in persistent or significant disability or incapacity, or

e. consists of a congenital anomaly or birth defect.

f. Is otherwise "medically significant" (e.g., that it does not meet preceding criteria, but is considered serious because treatment/intervention would be required to prevent one of the preceding criteria).

Initial or follow-up SAE information must be reported within 24 h of knowledge by submitting an initial or follow-up SAE report via email or fax to Diamond PV:

Fax: +44 (0) 1279 418 964

Email: pvservices@diamondpharmaservices.com

SAE(s) will be collected throughout the study from the signature of participant informed consent through to the post-study follow-up visit. Serious adverse reactions (SARs) occurring after the follow-up period should be reported to Diamond if the Investigator becomes aware of them.

The SAE Form must be completed as fully as possible with information relevant to the SAE(s) being reported. If it is not possible to complete all sections of the SAE Form within 24 h, transmission of the form must not be delayed, and the outstanding information should be sent on a follow-up SAE Form.

Diamond PV will notify the Sponsor and relevant personnel of the SAE via e mail within 1 business day of receipt of the initial SAE report.

AEs which meet all of the following criteria

- Serious
- Unexpected (i.e., is not consistent with the applicable product information e.g., IB for an unapproved IMP or SmPC for an authorised product)
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product

will be classified as suspected unexpected serious adverse reactions (SUSARs) and should be reported to the REC and to the MHRA in accordance with applicable regulatory requirements for expedited reporting. Diamond PV will report SUSARs to the REC and MHRA on behalf of the Sponsor as per the regulatory timeline.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Monitoring of Participants with Adverse Events

In the event of any abnormalities considered to be clinically significant by the investigating physician, participants will be followed up with appropriate medical management until:

- It has resolved/returned to normal or baseline.
- The event has stabilised at a level acceptable to the Investigator and is not considered to be clinically significant.

Pregnancy

Pregnancies must be reported within 24 h of first knowledge by submitting a pregnancy notification form via email or fax to Diamond PV following the same procedures described for SAEs reporting and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Once consent has been obtained, pregnancy outcomes must be collected for females who received GBS-NN/NN2 and should be sent to Diamond PV within 24 h of the time the information is known. Consent to report information regarding pregnancy outcomes should be obtained from the mother. Pregnancy in itself is not regarded as an AE.

If the pregnancy outcome meets the SAE definition also complete an SAE Form. It is important to monitor the outcome of any pregnancies of participants in order to provide SAE data on congenital anomalies, birth defects or spontaneous abortion.

10.7.1.4.2 Laboratory Safety Assessments

Laboratory safety screen samples will be analysed by Simbec-Orion Laboratory Services or at an appropriate referral laboratory. Printed laboratory test result reports will include normal reference ranges. A decision regarding whether the laboratory test result outside the normal reference range is of clinical significance or not shall be made by an Investigator/designee and the report will be annotated accordingly. Clinically significant laboratory test result abnormalities will be recorded on the AE page. The normal reference ranges for laboratory test parameters will be detailed in the SLPDoc0024 Normal Reference Ranges and Alert Reference Values document.

Biochemistry Tests: Sodium, potassium, chloride, bicarbonate, blood urea, creatinine, creatine kinase, glucose, calcium, albumin, cholesterol, C- reactive protein (CRP), triglycerides, phosphorus (inorganic phosphate), lactate dehydrogenase (LDH), total protein, globulin, uric acid, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total bilirubin and direct bilirubin.

Blood samples for biochemistry analyses for each time-point will be collected into an appropriately sized serum collection tube with or without a separator, and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses. Assessments of blood sample quality (i.e., for sample verification) will be performed by measuring 3 indices [namely, Lipaemic (for Lipaemia), Haemolytic (for Haemolysis) and Icteric (for Icterus)] in serum.

Haematology Tests: Red blood cell (erythrocyte) count, haemoglobin, HCT, platelet count, white blood cell (leukocytes) count with absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils which are reported in absolute and percentage values).

Blood samples for haematology analyses for each time-point will be collected into an appropriately sized blood collection tube containing ethylenediaminetetraacetic acid (EDTA)

and analysed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

Urinalysis Tests: Specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrites.

A mid-stream urine sample for each time-point will be collected into a 30 mL collection/storage container. Urinalysis will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/manual kit(s)/method(s) of analyses.

In the event that the urinalysis 'dipstick' test result is positive for nitrite and/or 2+ or more reported for protein, blood, and/or leucocytes, then urine microscopy will be performed by reflex. The following test parameters will be reported: bacteria, casts (non-pathogenic), casts (pathogenic), crystals, epithelial cells, red blood cells and white blood cells. The urine microscopy will be performed by Simbec-Orion Laboratory Services, or at an appropriate referral laboratory, using an appropriate analyser/method(s) of analyses.

10.7.1.4.3 Other Safety Assessments

Vital signs: Supine systolic/diastolic blood pressure, heart rate, tympanic temperature and respiration rate.

Measurements will be recorded in the supine position after 5 min of participants lying supine. Blood pressure, heart rate and temperature will be measured by the DINAMAP* Compact Vital Signs Monitor (Model TS) or equivalent. Normal ranges for vital signs are presented in Appendix 1.

Physical Examination

A physical examination will be performed by an Investigator. The examination will include ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system, lymph nodes and musculoskeletal). An Investigator can examine other body systems if required, at their discretion.

12-lead Electrocardiogram (ECG): Heart rate, PR interval, QRS width, QT interval and QT interval corrected using Fredericia's formula (QTcF).

Measurements will be recorded in the supine position after 10 min of participants lying supine. 12-lead ECG recordings will be made using a Mortara ELI280 or equivalent. Each ECG trace should be labelled with the study number, participant number, year of birth. An Investigator will provide an interpretation of each tracing. Clinically significant abnormalities will be recorded on the AE page. Normal ranges for 12-lead ECG parameters are presented in Appendix 1.

Concomitant Medication

All prior and concomitant medications taken during the study will be recorded in the participant's eCRF (see Section 10.6.10).

Injection Site Assessment

Injection site tolerability assessments will be performed to assess local reactogenicity at injection site for any evidence of a reaction (redness, bruising, induration, itching and pain) and to record the diameter (cm) of the reaction.

10.7.2 Appropriateness of Measurements

All measurements performed in the study are standard measurements.

The total volume of blood to be collected from each participant during the study (approximately 418 mL) is considered acceptable (Table 10.7.2).

Table 10.7.2 Summary of Blood Volume

Procedure	Visit	Number of Samples	Blood Volume per Sample (mL)	No. Treatment Periods	Blood Volume (mL)
Biochemistry	Screening[1]	1	4.5	N/A	4.5
	Day 8	1	4.5	N/A	4.5
	Day 29	1	4.5	N/A	4.5
	Day 57	1	4.5	N/A	4.5
	Post-study	1	4.5	N/A	4.5
Haematology	Screening[1]	1	3	N/A	3
	Day 8	1	3	N/A	3
	Day 29	1	3	N/A	3
	Day 57	1	3	N/A	3
	Post-study	1	3	N/A	3
PD blood sample – antibody response	Treatment Period	6	20	N/A	120
Exploratory blood sample – [redacted]	Treatment Period	2	40	N/A	80
Blood sample for future work	Days 29/57/85	3	60	N/A	180
				Total Blood Volume[2]	418

[1] From the biochemistry blood sample collected at the Screening visit, the serum pregnancy test, serum FSH (for postmenopausal participants only) and virology screen will be analysed from the same serum sample.
[2] Please note: This total blood volume does not include any additional blood sample collection(s) for retest, unscheduled testing or additional tests required at the discretion of the Investigator/designee. The exact volumes of each sample may change but the total volume of blood drawn for any participant will not exceed 450 mL.
PD = pharmacodynamic

10.7.3 Primary Efficacy Variable(s)

Not applicable.

10.7.4 Drug Concentration Measurements

Not applicable.

10.7.5 Pharmacodynamic Assessments

10.7.5.1 Antibody Response

PD blood sampling for antibody response assessments (antibody concentration specific for GBS-NN/GBS-NN2 and antibody concentration specific for AlpCN, RibN, Alp1N and Alp2/3N) will be collected during the study at the time points specified in Table 10.7.1.

Blood samples (20 mL [2x10 mL samples]) will be taken into serum tubes at each time point, processed as described in the Sample Handling Manual.

Aliquots for GBS-NN/GBS-NN2 antibody response assessments will be analysed at Simbec-Orion Laboratory Service using a validated assay according to applicable local SOPs.

Aliquots for AlpCN, RibN, Alp1N and Alp2-3N antibody response assessments will be analysed at a laboratory contracted by MinervaX.

10.7.5.2 Additional Exploratory Assessments

Blood samples for additional exploratory assessments [redacted] will be collected during the study at the timepoints specified in Table 10.7.1.

Blood samples (40 mL [4x10 mL samples]) for [redacted] assessment will be taken into [redacted] at each time point, processed as described in the Sample Handling Manual. [redacted] will be shipped to MinervaX's Laboratory, address: ATT: [redacted], Immunology Section, Lund University, BMC D14, 22184 Lund, Sweden for analysis using validated assays according to applicable local SOPs.

Additional exploratory assessments will be reported separately.

10.7.6 Other Assessments

Blood samples for future validation and calibration work will be collected during the study at the time points specified in Table 10.7.1.

Blood samples (60 mL [6x10 mL samples]) will be taken into serum tubes at each time point, processed as described in the Sample Handling Manual.

Serum aliquots for future validation and calibration work will be shipped to MinervaX AB, Scheelevägen 22, 223 63 Lund, Sweden.

10.8 Data Quality Assurance

At the time the study is initiated, a representative of the Sponsor will thoroughly review the final protocol and eCRFs with the Principal Investigator and site staff. During the course of the study the Monitor will visit the Clinical Unit regularly to check the completeness of the participants' records (including the volunteer (participant) master files, laboratory and 12-lead ECG print-outs), the accuracy of entries into the eCRFs, the adherence to the final protocol and to ICH GCP E6 (R2) guidelines[1], the progress of enrolment and also to ensure the storage, handling and accountability of the IMP. The Principal Investigator and key study personnel will be available to assist the Monitor during these visits.

The Principal Investigator will give the Monitor, Auditor(s), the REC, and the MHRA direct access to relevant clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the participants will leave Simbec-Orion. The Sponsor will maintain the confidentiality of all participant records, in line with Section 6.10 of the ICH GCP E6 (R2) guidelines[1].

Study data will be fully documented in the eCRFs and study logbooks. Dated signatures will be given to account for all interventions in the study by research staff.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

For the purposes of this study the source data will be recorded as detailed in Table 10.8.1.

Table 10.8.1 Summary of Source Documentation Location

Data	Source Document			
	Volunteer Master File	eCRF[1]*	Clinic Source File	Other Study Documentation
Evidence of healthy participant status/primary disease condition for entry into clinical study	X			
Demographic data (e.g., age, year of birth, gender)	X			
Demographic data (e.g., race, ethnicity, height, weight, and BMI)		X		
Medical history	X			
Inclusion and exclusion criteria			X	
Informed consents[2]				X
Participant involvement in the clinical study		X		
Screening number				X (screening log)
Participant number				X (enrolment log)
AEs		X		
SAEs				X (SAE form)
Pregnancies				X (Pregnancy notification and outcome form)
Previous and on-going therapy	X			
Concomitant medication		X		
Results of study examinations (e.g., 12-lead ECGs and laboratory safety tests)[3]			X	
Vital Signs		X		
Physical Examination[4]		X		
Study visit dates		X		
Administration of IMP		X		
Blood PD and Exploratory sample collection times		X		
Blood safety sample collection times			X (test request form)	
Urine safety sample collection times (including start and stop times of collection intervals and volumes)			X (test request form)	
Injection site reaction photograph if needed				X (Photograph)
Temperature, Injection Site Reactions, General Reactions, AE and concomitant medication diaries				X (Participant Diary Cards)
Evidence for participation and treatment allocation in MVX0002	X			X (MVX0002 enrolment log and randomisation codes)

1 In the event staff are unable to enter data directly into the eCRF (e.g., technical/internet issues), data will be entered directly into a back-up paper source workbook at the time of assessment, then transcribed and subsequently QC'd.

2 The original ICFs will be maintained in the study officer file during the clinical phase and will then be transferred to the Project Manager for archiving with the Investigator Site File (ISF) at the end of the study.

3 The 12-lead ECG trace and laboratory safety test print-out including medical review will be stored in the Clinic Source File.

4 In the eCRF, the date and time of each physical examination will be recorded. Any abnormal findings will be captured on the Medical History form at Screening and as an Adverse Event during clinical conduct.

AE = adverse event, eCRF = electronic case report form, ECG = electrocardiogram, IMP = investigational medicinal product, PD = pharmacodynamic, SAE = serious adverse event

The above table indicates where source data will be recorded but for completeness the following information will also be recorded in the volunteer master file:

- Clinical study code.
- Study visit dates (pre-dose; post-dose).
- IMP administration (date of dose).
- Results of any key safety and efficacy measures from the clinical study that, in the opinion of an Investigator, should be noted.
- Any concomitant medications used to treat the participant during the study that, in the opinion of an Investigator, should be noted.

The data collected in the eCRFs during the study will be subject to quality control checking by clinical staff prior to sign off.

Designated investigator site staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Staff will not be given access to the eCRF until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Biometrics group. The Investigator must certify that the data entered into the eCRF are complete and accurate.

The study will be subject to an independent audit by the Simbec-Orion Quality Assurance Unit as outlined in Simbec-Orion SOP GRP-QA 002.

Independent clinical quality assurance audits may be performed at any time during or following completion of the study by the Sponsor, or its authorised agents, and Regulatory Authorities and/or the REC.

10.9 Statistical Methods and Determination of Sample Size

10.9.1 Statistical and Analytical Plan

A statistical analysis plan (SAP) will be written by Simbec-Orion and agreed by MinervaX ApS prior to the locking of the database and subsequent reporting of the study data.

10.9.2 Study Variables/Endpoints

Primary Endpoints

- The following endpoints will be evaluated to assess the safety over 12 weeks of a single dose (booster or first dose) of the GBS vaccine (GBS-NN/NN2): local and systemic reactogenicity; AEs; laboratory tests; urinalysis; vital signs; physical examination.

Secondary Endpoints

- The following secondary **safety endpoints** will be evaluated to assess the long-term safety profile of the GBS-NN/NN2 vaccine 6 months following the dose (booster or first dose): the incidence of autoimmune diseases and/or clinically relevant medical events related to the vaccination that occur in the 6-month follow-up period.
- The following secondary immunological endpoints will be evaluated.

- Individual participant antibody concentration specific for GBS-NN and GBS-NN2, in µg/mL, at 0 and 84 days after the dose (booster or first dose).
- Individual participant antibody concentration specific for AlpCN, RibN, Alp1N and Alp2-3N, in µg/mL, at 0, 14, 28, 56, 84 and 182 days after the dose (booster or first dose).

From the endpoints listed above the following will be derived:

- Geometric mean fold increase in antibody concentration, specific for GBS-NN and GBS-NN2, between Day 1 and Day 85.
- Geometric mean fold increase in antibody concentration, specific for AlpCN, RibN, Alp1N and Alp2-3N, between Day 1 and Days 8, 29, 57, 85 and 183.
- Proportion of participants achieving antibody concentrations, specific for AlpCN, RibN, Alp1N and Alp2-3N, above 0.5, 1, 2, 4 µg/mL, 7, 28, 56, 84 and 182 days after receiving the dose (booster or first dose).

The secondary endpoints relating to antibody concentrations specific for AlpCN, RibN, Alp1N and Alp2-3N and all exploratory endpoints will be analysed and reported separately. Full details of the analyses will be documented in a separate plan(s).

The values of these endpoints on Day 85 will be the basis of the primary immunological analysis; this timepoint is anticipated to be the time of delivery after vaccination in a pregnant woman.

10.9.3 Analysis Sets

Safety Set (SAF): All enrolled participants who receive the study vaccine will be included in the Safety Set. This analysis set will be used for baseline and safety summaries as well as for all study listings.

Immunogenicity Set (IG): The subset of participants who will receive the study vaccine with available post-vaccination titres.

Per Protocol Set (PP): All participants included in the IG Set who do not violate the protocol in a way that may invalidate or bias the results.

The immunological analyses will primarily be performed on the IG Set but will also be performed on the PP set if the number of participants in the PP set differs by more than 5% from that of the IG Set.

10.9.4 Description of Statistical Methods

All statistical analysis will be performed using SAS® (the most up to date version will be used and this will be documented in the SAP).

10.9.4.1 Demographic and Background Data

All demographic and background data will be listed, in addition:

Disposition: Participant disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of participants dosed, completed and prematurely discontinued (including reason for discontinuation) from the study will be summarised.

Additionally, the number and percentage of participants within each analysis set will be summarised.

Demographics: Demographic data will be listed. Descriptive statistics (number of participants in the analysis set (N), number of participants with non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum) will be tabulated for the continuous variables age, height, weight and BMI and frequencies (number and %) for the categorical variable race.

Demographic data will be listed and summarised using the Safety Set. Demographic characteristics will be also presented for other analysis sets (immunogenicity and/or per-protocol) if they differ from the Safety Set.

10.9.4.2 Efficacy Data

Not applicable.

10.9.4.3 Safety Data

All safety data will be listed, in addition:

AEs: All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the most up to date version that is available at the time of database build will be used and will be listed in the Data Management Plan). The MedDRA dictionary will not be updated during the course of the study.

All AEs occurring up to and including Day 85, including those which occurred prior to dose of IMP, will be listed. Only treatment emergent adverse events (TEAEs), i.e., existing conditions that worsen or events that occur during the course of the study after administration of IMP, will be included within the summary tables.

An overall summary of AEs will be produced including the number of TEAEs; the number and % of participants reporting at least 1 TEAE, serious TEAE, TEAE leading to withdrawal from the study; the number and % of participants reporting TEAEs by severity and relationship to IMP.

The number of TEAEs and the number and % of participants reporting at least 1 TEAE will be tabulated by system organ class (SOC) and preferred term. A participant reporting multiple episodes of a particular AE within a treatment period will only contribute 1 count towards the corresponding SOC and preferred term.

The number of TEAEs and the number and % of participants reporting at least 1 TEAE will be tabulated by preferred term and sorted by descending frequency on the total number of participants with that AE. A participant reporting multiple episodes of a particular AE within a treatment period will only contribute 1 count towards the corresponding preferred term.

In addition, the number and % of participants reporting TEAEs will be tabulated by maximum severity and strongest relationship to IMP. For the summary of TEAEs by severity, if a participant has multiple events occurring within the same SOC or preferred term the event with the highest severity will be counted. Similarly, for TEAEs by relationship to IMP, if a participant has multiple events occurring within the same SOC or preferred term, the event with the highest association to IMP will be counted.

Additionally, the above listings and summaries will be presented separately for autoimmune diseases and/or clinically relevant medical events related to the vaccination that occur in the 6-month (182 days) follow-up period, and systemic and local reactogenicity TEAEs (as defined in the SAP) occurring up to and including Day 85.

Physical examination: Physical examination results will be listed.

Laboratory Safety: Biochemistry, haematology, and urinalysis parameters will be listed with any out of normal range values flagged. Laboratory test results which are out of normal range will also be presented separately along with normal reference ranges. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Screening) biochemistry and haematology parameters at each time point up to and including Day 85 will be tabulated.

Vital Signs: Vital signs parameters will be listed with any out of normal range values flagged. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (Day 1 pre-dose) values at each time-point will be tabulated.

Injection Site Reactions: A summary of injection site reactions will be produced by visit and category (redness, bruising, induration, itching and pain), including the number and percentage of participants in each category.

10.9.4.4 Pharmacokinetic Data

Not applicable.

10.9.4.5 Pharmacodynamic Data

Immunogenicity will be assessed using the Immunogenicity Set and will be repeated for the Per Protocol Set, should the analysis sets differ.

Antibody Response: Antibody titre responses (IgG concentrations [specific for GBS-NN and GBS-NN2]) will be listed along with the Day 1 and Day 85 results obtained from the MVX0002 study. Antibody response data will be summarised descriptively using N, geometric mean and 95% confidence interval (CI) for the geometric mean, , minimum, median, maximum and IQR (interquartile range), by study (MVX0003, MVX0002) and dose level received in the MVX0002 study (placebo/vaccine naïve, 25ug, 50ug) and active doses pooled. Individual and geometric mean plots of antibody concentrations will also be produced by study and dose level received in the MVX0002 study.

In order to explore the decline in IgG antibodies since the previous study, a statistical comparison of the GBS-NN and GBS-NN2 antibody concentrations on Day 1 of the MVX0003 study and Day 85 of the MVX0002 study will be performed for each of the corresponding MVX0002 dose levels and active doses pooled. Following logarithmic transformation, antibody concentrations will be subjected to a mixed effect analysis of variance (ANOVA), with study as a fixed effect and participant as a random effect. Point estimates and 95% confidence intervals will be constructed for the contrasts between Day 1 (MVX0003) and Day 85 (MVX0002). The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric least squares means (LSMeans) and corresponding 95% CIs for each MVX0002 dose level and all active doses pooled.

A similar ANOVA will also be performed in order to compare the Day 85 GBS-NN and GBS-NN2 antibody concentrations for the MVX0003 study to those obtained for the MVX0002 study, for each of the corresponding MVX0002 dose levels and all active doses pooled.

Additionally, the GBS-NN and GBS-NN2 antibody concentrations observed on Day 85 of the MVX0003 study will be compared between participants who received 25ug GBS-NN/GBS-NN2 in the previous study and placebo/vaccine-naïve participants, between participants who received 50ug GBS-NN/GBS-NN2 in the previous study and between placebo/vaccine-naïve participants and the participants who received either active dose (25ug and 50ug pooled) in the previous study and placebo/vaccine-naïve participants. Following logarithmic transformation, Day 85 antibody concentrations will be subjected to an analysis of variance (ANOVA), with dose level as a fixed effect. Point estimates and 95% CIs will be constructed for the contrasts between the dose levels. The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric LSMeans and corresponding 95% CIs.

The fold-increase in antibody concentrations specific for GBS-NN and GBS-NN2 will be derived between:

- Day 1 and Day 85 for both the MVX0002 and MVX0003 studies, for each of the corresponding MVX0002 dose levels and all active vaccines pooled.

- Day 85 of the MVX0002 study and Day 85 of the of the current MVX0003 study, for each of the corresponding MVX0002 dose levels and all active vaccines pooled.

Fold-increases will be listed and descriptive statistics (N, n, geometric mean and corresponding 95% CI, minimum, median, maximum and IQR) will be tabulated by study and MVX0002 dose level and all active vaccines pooled.

In addition, the proportion of participants with concentrations above the pre-determined thresholds of 1, 2, 4 and 8 µg/mL at Day 85 will be presented by study and MVX0002 dose level and all active vaccines pooled.

10.9.4.6 Other Data

- Individual participant antibody concentration specific for AlpCN, RibN, Alp1N and Alp2-3N will be analysed and reported separately.
- Additional exploratory assessments for exploratory objectives including [redacted] results will be analysed and reported separately.

10.9.5 Sample Size Calculation

Sample size calculation has not been assessed. It is limited by the number of participants who have participated in study MVX0002 and are willing to participate for this study. A minimum of 30 and a maximum of 40 female participants will be recruited, comprised of between 20 and 30 participants who had received previous vaccination with GBS-NN/NN2 in the MVX0002 study and up to 10 participants who had received placebo in the MVX0002 study. If an insufficient number (<5) of previous placebo recipient participants return to this study, vaccine naïve participants will be recruited.

11 PRACTICAL CONSIDERATIONS

11.1 Storage of Data

The ISF and associated study documentation will be archived for at least 25 years after the end of the study (last participant last visit) as per European Medicine Agency Guideline INS/GCP/856758/2018[266]. The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of Simbec-Orion.

The Sponsor has delegated the set up and maintenance of the Sponsor electronic Trial Master File (eTMF) to Simbec-Orion. The eTMF will be returned to the Sponsor at the end of the study, who will archive it for at least 25 years after the end of the study.

11.2 Protocol Amendments

Changes in the study protocol must take the form of written protocol amendments and shall require the approval of all persons responsible for the study (see Section 1).

A protocol amendment is deemed to constitute a substantial protocol amendment if it is considered to be likely to affect to a significant degree either:

a. The safety or physical or mental integrity of the participants of the study.
b. The scientific value of the study.
c. The conduct or management of the study.
d. The quality or safety of any IMP used in the study.

Such amendments must be submitted to the REC responsible for the study and the MHRA for approval prior to implementation.

Protocol amendments required for urgent safety reasons may be implemented immediately. However, the REC and MHRA must be notified in writing within 3 days of the measures taken and the reasons for implementation.

All other amendments shall be deemed to be non-substantial and as such do not need the prior approval of the REC and the MHRA.

11.3 Confidentiality

The confidentiality of the study must be maintained at all times and the Principal Investigator must not reveal any information relating to the study without express permission from the study Sponsor.

11.4 Study Report and Publication Policy

The Principal Investigator will obtain the Sponsor's written permission before any information concerning this study is submitted for publication.

11.5 General Data Protection Regulation (GDPR)

Personal data of the participants shall be processed in a manner that ensures it has appropriate security. This includes protection against unauthorised or unlawful processing and against

accidental loss, destruction or damage and by using appropriate technical or organisational measures. One such measure is by the Investigator ensuring that the participants' personally identifiable information should be replaced through the use of pseudonymisation.

On the eCRFs or other documents submitted to MinervaX ApS, Simbec-Orion participants will NOT be identified by their names but by the assigned participant number (panel/screening/participant number) to ensure confidentiality of the participants' information and that data minimisation principles are maintained. If participant names are included in error on copies of documents submitted to MinervaX ApS, Simbec-Orion participants', the names (except for initials) will be erased or securely destroyed and the assigned participant number added to the document.

12 REFERENCES

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APPENDIX 1: NORMAL RANGES FOR VITAL SIGNS AND ECG PARAMETERS

Vital Sign Parameters		
Parameter	**Normal Range**	**Units**
Heart Rate	40-100	beat(s) per minute (bpm)
Systolic Blood pressure	90-140	millimetre(s) of mercury (mmHg)
Diastolic Blood pressure	50-90	millimetre(s) of mercury (mmHg)
Respiratory Rate	12-18	breath(s) per minute
Tympanic Temperature	35.0-37.5	degrees Celsius (ºC)

ECG Parameters		
Parameter	**Normal Range**	**Units**
Heart Rate (HR)	40-100	beat(s) per minute (bpm)
PR Interval	120-220	millisecond(s) (ms)
QRS Width	70-120	millisecond(s) (ms)
QT Interval	N/A	N/A
QTc Interval (Fridericia's Formula)	Male: 350-450 Female: 350-450	millisecond(s) (ms) millisecond(s) (ms)

APPENDIX 2: DECLARATION OF HELSINKI (BRAZIL, 2013)

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for medical-research-involving-human-subjects/