Statistical analysis plan

A multicentre, multinational, parallel group, observer-blind, randomised, placebo-controlled study on the Group B Streptococcus vaccine (GBS-NN/NN2), investigating the immunogenicity and safety of four vaccination regimens in pregnant woman, assessing IgG specific to AlpN proteins in cord blood and maternal blood, and the safety profile in mother and infant up to 6 months post-delivery

Final

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List of abbreviations and definition of terms

ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
Alp	Alpha like protein family; Rib, Alp1, AlpC, Alp2, Alp3 and Alp4.
BA	Bivariate analysis
BIG	Baby immunogenicity set
BMI	Body mass index
BPP	Baby per protocol set
BSA	Baby safety analysis set
CI	Confidence interval
CM	Concomitant medication
CRO	Clinical research organisation
CS	Clinically significant
CV	Coefficient of variation
DK	Denmark
eCRF	Electronic case report form
eDiary	Electronic diary
EOD	Early-onset disease
EudraCT	(European Union Drug Regulating Authorities Clinical Trials) European Clinical Trials Database
GA	Gestational age
GBS	Group B Streptococcus
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMCR	Geometric mean concentration ratio
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
ITT	Intention-to-treat
LOD	Late-onset disease
MAAE	Medically attended adverse event
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean capsular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIG	Maternal immunogenicity analysis set
MPP	Maternal per protocol analysis set
NN	Fusion protein based on N-terminal domains of RibN and AlpC surface proteins
NN2	Fusion protein based on N-terminal domains of Alp1 and Alp 2/3 surface proteins
[redacted]	[redacted]
PI	Principal investigator

PP	Per protocol
Rib	Protein expressed on the surface of GBS
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
TLF	Tables, listings and figures
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UK	United Kingdom
WHO	World Health Organization

1 Introduction

This document describes the planned statistical analyses for the GBS-NN/NN2 Study with the Study ID MVX0004 and is an elaboration on the analysis outlined in protocol version 5.0 dated 14-Apr-2023 [1].

Group B Streptococcus (GBS) is a widely distributed commensal, which can colonize the vagina of pregnant women and on occasion provoke invasive GBS disease like sepsis, pneumonia and meningitis in infants. Global incidence is thought to be about 0.5 per 1000 live births, but with large geographical variation. Neonatal infections will typically occur within the first 3 months. A distinction is conventionally made between EOD 'type' (occurrence days 1-6) and LOD (days 7-89). In principle infections could thus be prevented by vaccination of the pregnant mother by which the antibody is passively transferred to the fetus (Brechje de Gier et al. 2019 [2]).

Most women already have a variety of naturally occurring antibodies against GBS antigens. IgG is the most relevant antibody class in terms of immunity. These can be induced by a family of GBS surface proteins, called Alp-proteins. These proteins are anchored in the cell membrane through certain components, one of which is a functionally active N-terminal domain which facilitate invasion of epithelial cells and crossing of the blood-brain barrier. So far, six members of the Alp-proteins have been characterized (Rib, AlpC, Alp1, Alp2, Alp3, Alp4), of which 4, i.e., RibN, Alp1N, Alp2N, and AlpCN, are included in the MinervaX vaccine through 2 fusion proteins, GBS-NN and GBS-NN2, each containing 2 of the N-terminal domains mentioned above. The focus of this protein vaccine study is on the antibody level in the blood of mother and child alike. The risk of a high concentration of the GBS organism in the baby blood is reduced by increasing the concentration of the IgG antibodies which are transferred across the placenta to the infant in utero.

1.1 Study objectives and endpoints

In this section, objectives of the study together with their corresponding endpoints are presented as written in the protocol version 5.0, dated 14-Apr-2023.

1.1.1 Objectives

1.1.1.1 Primary objective: immunogenicity

The primary objective of this study is to compare the concentrations of IgG specific to the AlpN proteins (RibN, Alp1N, Alp2N and AlpCN) in cord blood from babies, born to women who received the GBS-NN/NN2 vaccine or placebo, between four vaccination regimens during pregnancy, between the GBS-NN/NN2 and placebo groups:

- Group 1: GBS2 doses GBS-NN/NN2 at 26 & 30 weeks GA, placebo at week 22
- Group 2: 2 doses GBS-NN/NN2 at 22 & 26 weeks GA, placebo at week 30
- Group 3: 2 doses GBS-NN/NN2 at 22 & 30 weeks GA, placebo at week 26
- Group 4: 1 dose GBS-NN/NN2 at 26 weeks GA, placebo at weeks 22 & 30

Furthermore, a pure placebo group (with half the number of subjects) has been added for general reference:

- Group 5: Placebo at 22, 26 & 30 weeks GA

1.1.1.2 Key secondary objective: safety

To evaluate the safety and tolerability of the GBS-NN/NN2 vaccine in pregnant women from 22 (±1) weeks GA and to evaluate developmental milestones in the baby up to 6 months post-delivery.

1.1.1.3 Secondary objectives: Immunogenicity

To compare the concentrations of IgG, specific to the AlpN proteins (RibN, Alp1N, Alp2N and AlpCN) in maternal blood at delivery, from women who received the GBS-NN/NN2 vaccine or placebo, according to four vaccination regimens during pregnancy, between the GBS-NN/NN2 and placebo groups (same groups as specified under primary objective).

Other secondary immunogenicity objectives are:

- To compare the concentrations of IgG specific to the AlpN proteins, in maternal blood at 4 weeks after each dose of vaccine/placebo for the different vaccination regimens
- To evaluate the ratios of antibody concentrations between maternal and cord blood at delivery
- To evaluate the concentrations of IgG specific to the AlpN proteins, up to 3 months post-delivery, in infant blood

1.1.1.4 Exploratory objectives

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

1.1.2 Endpoints

1.1.2.1 Primary endpoints

The following primary endpoint(s) will be evaluated, by vaccination group:

- Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in cord blood from each baby:
    - The geometric mean (coefficient of variation [CV]) antibody concentrations at birth will be calculated
    - The proportions of babies who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at birth will be calculated.

If cord blood cannot be obtained, venous infant blood may be collected within 72 hours of birth and will in that case be considered a valid substitute for the cord blood sample.

1.1.2.2 Key secondary endpoints: safety

The following key safety secondary endpoint(s) will be evaluated in the mother:

Local and systemic reactogenicity and adverse events:

- Solicited injection site reactions following the vaccinations
- Solicited systemic adverse events following the vaccinations
- All other adverse events following the vaccinations
- Laboratory tests; urinalysis; vital signs (heart rate, blood pressure, oral body temperature); physical examinations

The following key safety secondary endpoint(s) will be evaluated in the baby:

- Gestational age; weight; length; head circumference; Apgar score at 1, 5 and 10 minutes
- Developmental milestones at 6 months of age
- Adverse events: MAAEs, AEs of special interest (AESI) or SAEs, and CMs prescribed for such events

1.1.2.3 Secondary endpoints: Immunogenicity

The following secondary immunogenicity endpoints will be evaluated, by group and time-point:

- Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in maternal blood:
    - The geometric mean (CV) antibody concentrations at delivery, and geometric mean concentration ratios relative to baseline will be calculated.
    - The proportions of mothers who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at delivery will be calculated.
    - The geometric mean (CV) antibody concentrations at 4 weeks after each dose of vaccine/placebo and geometric mean concentration ratios relative to baseline will be calculated.
- The ratios of antibody concentrations measured in maternal blood and cord blood respectively at delivery will be derived

The following immunogenicity endpoints will be evaluated in the baby:

- Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in blood from each baby at 1 month and 3 months of age:
    - The geometric mean (CV) antibody concentrations at 1 month and 3 months after birth will be calculated.
    - The proportions of babies who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at 1 month and 3 months after birth will be calculated.

1.1.2.4 Exploratory endpoints

The following exploratory immunogenicity endpoints will be evaluated:

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

2 Study design

According to the protocol version 5.0, dated 14-Apr-2023, this is a phase II, multicentre, multinational, parallel group, observer-blind, randomised and placebo-controlled study on the Group B Streptococcus vaccine (GBS-NN/NN2), investigating the immunogenicity and safety of four vaccination regimens in healthy, pregnant women, assessing IgG specific to AlpN proteins in cord blood and maternal blood, and the safety profile in mother and baby up to 6 months post-delivery.

2.1 Overview of study procedures

The study will comprise subjects from sites in 3 countries DK: 3 sites, UK: 2 sites, ZA: 5 sites. Mothers will be assigned to groups as shown in Table 1.

Table 1. Overview of assignment to groups

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
No. Subjects	60	60	60	60	30
GA 22 (±1) weeks	PLACEBO (saline)	GBS-NN/NN2	GBS-NN/NN2	PLACEBO (saline)	PLACEBO (saline)
GA 26 (±1) weeks	GBS-NN/NN2	GBS-NN/NN2	PLACEBO (saline)	GBS-NN/NN2	PLACEBO (saline)
GA 30 (±1) weeks	GBS-NN/NN2	PLACEBO (saline)	GBS-NN/NN2	PLACEBO (saline)	PLACEBO (saline)

2.2 Study visits and assessments

Visits and assessments are performed as presented in Tables 2 and 3 below, for mothers and babies, respectively. A description of individual study visits can be found in Section 4.3.2 of the protocol version 5.0, dated 14-Apr-2023.

Table 2. Study visits and assessments for mothers

	Screening Period	**Treatment and follow-up Period**										
	Screening	**Visit 1**	**Visit 2[i]**	**Visit 3**	**Visit 4[i]**	**Visit 5**	**Visit 6[i]**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Assessment	Day -14 to Day -1	Day 0 21+0 to 23+6 weeks GA	Day 3-5	Day 26-30	Day 31-33	Day 54-58	Day 59-61	Day 82-86	Delivery up to 72 hours after delivery	24-32 days post-delivery	84-96 days post-delivery	166-194 days post-delivery
Informed consent	X											
Inclusion/exclusion criteria	X											
Demography	X											
Medical and obstetric history	X											
Physical examination[e]	X	X		X		X				X		X
Obstetric examination	X	X	X	X	X	X	X	X				
Height[l], weight, BMI	X							X		X		X
Vital signs[a]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X	X	X
Urinalysis	X	X		X		X			X	X		
Ultrasound result[c]	X											
Safety laboratory tests[d]	X		X	X	X	X	X	X				
Hep B, Hep C, HIV and syphilis[m]	X											
Eligibility check		X										
Randomisation		X										
Contraindications vaccination check				X[j]		X[j]						
Immunogenicity blood sample		X Predose		X Predose		X Predose		X	X			
Vaccine/placebo administration		X		X		X						
Assessment of injection site and immediate AEs[f]		X	X	X	X	X	X	X				
Instruct 7-day-eDiary		X		X		X						
Review eDiary and transfer data incl.			X	X	X	X	X	X				

	Screening Period	Treatment and follow-up Period										
	Screening	**Visit 1**	**Visit 2[i]**	**Visit 3**	**Visit 4[i]**	**Visit 5**	**Visit 6[i]**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Assessment	Day -14 to Day -1	Day 0 21+0 to 23+6 weeks GA	Day 3-5	Day 26-30	Day 31-33	Day 54-58	Day 59-61	Day 82-86	Delivery up to 72 hours after delivery	24-32 days post-delivery	84-96 days post-delivery	166-194 days post-delivery
AE/CM												
[redacted]									X	X	X	
Urine pregnancy test												X[g]
AE check	X								X[h]			
CM check	X								X[h]			

Footnotes

a. Heart rate, blood pressure and oral temperature.
b. Vital signs at vaccination visits will be recorded pre-dose and at 30 min post-dose prior to discharge.
c. Last available ultrasound results, as per UK, DK or SA schedules, for confirmation of no detectable congenital abnormalities and singleton pregnancy.
d. Haematology (red blood cell count, haemoglobin, haematocrit, platelet count, MCV, MCHC, white blood cell count with absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils counts) and biochemistry (sodium, potassium, blood urea, creatinine, creatine kinase, glucose, calcium, albumin, cholesterol, C-reactive protein, triglycerides, phosphorus (inorganic phosphate), lactate dehydrogenase, total protein, globulin, uric acid, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl-transferase, total bilirubin and direct bilirubin). If delivery before a scheduled safety laboratory test visit, it is performed at delivery.
e. Full physical examinations Screening & Visit 11. Targeted physical examinations remaining visits.
f. Photographs may be taken of injection site reactions as required. At vaccination visits (only), check immediate adverse reactions.
g. Any participant found to be pregnant at the end of the study will be followed up, as regards if their baby is healthy at delivery.
h. From Delivery (Visit 8) and onwards, only MAAEs, AEs of special interest (AESI), e.g., GBS disease, autoimmune disease and immune-mediated reactions, or SAEs, and CMs prescribed for such events are reported.
i. Visit 2, Visit 4, Visit 6 and Visit 9-11 may be home visits.
j. There is contraindications check at V3 (incl. assessment of safety laboratory tests from V2) and at V5 (incl. assessment of safety laboratory tests from V4) before the vaccinations.
k. Last available Hep B, Hep C, HIV and Syphilis results, as per UK, DK or SA schedules. Only if no results are available, new samples are taken.
l. Height measurement only at screening.
m. If a participant delivers after V1, but before completing all pre-delivery visits, additional safety laboratory tests are taken at Delivery (V8).

Table 3. Schedule of assessments for babies

	Visit 8	**Visit 9**	**Visit 10**	**Visit 11**
Assessment	Delivery up to 72 hours after delivery	24-32 days post-delivery	84-96 days post-delivery	166-194 days post- delivery
Demography	X			
Gestational history[a]	X			
Physical examination	X	X	X	X
Head circumference	X	X	X	X
Length	X	X	X	X
Weight	X	X	X	X
Apgar score[b]	X[b]			
Vital signs[c]	X	X	X	X
Developmental milestones[f]		X	X	X
Immunogenicity blood sample	X[d]	X[e]	X[e]	
AE check	X		X[g]	
CM check	X		X[g]	

Footnotes

a. Gestational age and gender
b. Apgar score at 1, 5 and 10 minutes if available (available scores will be collected, 'not recorded' will be an option)
c. Heart rate (actual, not Apgar score).
d. Cord blood or infant blood (heel prick or venous sample) within 48 hours of birth.
e. Heel prick or venous sample.
f. Age-appropriate developmental milestone check
g. After the first 28 days of age, only MAAEs, AEs of special interest (AESI), e.g., GBS disease and abnormal development according to developmental milestones, or SAEs, and CMs prescribed for such events until 180 days of age

2.3 Determination of sample size

2.3.1 Sample size calculations for Phase II

For the assessment of adequate sample size, data from the finalized phase I study MVX0002 has been considered. In that study, 23 healthy females of childbearing potential were exposed to double vaccination, one month apart, with the vaccine of the present study. The proportion of subjects with antibody concentrations above predefined cut-points (%), with the cut-points set to 0.5, 1.0, 2.0 and 4.0, are shown in Table 4.

Table 4. The proportion of subjects with antibody concentrations above prespecified cut-points (%), with the cut-points defined as 0.5, 1.0, 2.0 and 4.0

Antigen	Cut-point 0.5	Cut-point 1.0	Cut-point 2.0	Cut-point 4.0
Alp1-N	100.00	95.65	95.65	86.96
Alp2-N	100.00	95.65	95.65	91.30
AlpC-N	100.00	95.65	91.30	73.91
Rib-N	95.65	95.65	82.61	60.87

Although the cord-blood samples of MVX0004 are somewhat different from these samples derived from healthy adults, they are believed to be close enough for an analogy to hold.

Using the antigen-specific expected preliminary proportion of subjects achieving antibody concentrations above the cut-point = 1 µg/ml as basis, the power of the non-inferiority tests described in section 4.5 below, would be above 90 % if equal responses in the vaccination groups 1, 2 and 3 are assumed and a group size of 60 is assumed. For higher cut-points (2/4/8) this power will be smaller particularly for the IgG corresponding to the Rib-N protein.

2.4 Blinding

Each site PI will be able to unblind an individual subject. The blinding should only be broken in case of an emergency, and only if the knowledge obtained through the unblinding is assessed to be needed for the proper treatment or continued safety of the subject experiencing the emergency.

The pharmacovigilance responsible CRO will be able to unblind an individual subject prior to submitting an expedited report of a suspected unexpected serious adverse reaction (SUSAR) to a CA or IEC, if unblinding is required by the CA or IEC.

Whenever possible, the sponsor, MinervaX, should be consulted before the blind is broken by the site.

The unblinding of a subject by the site PI or the pharmacovigilance responsible CRO takes place through the unblinding module in the eCRF, to which the applicable parties will be given access.

If unblinding of a subject has taken place (intentionally or unintentionally), the sponsor must be informed immediately, and be provided with an explanation, and it must be considered to withdraw the unblinded subject from the study.

The information in this section is described in more detail in a study specific blinding manual.

During conduct of the study an unblinded DSMB will work independently from the blinded study team. Likewise, an interim/early efficacy analysis focused on unblinded immunogenicity data, and certain key safety data, will be conducted when Visit 8 has been completed for the last subject (baby). These activities involving unblinded personnel are described in further detail in section 6 below.

2.5 Randomization

In accordance with Table 1 above, patients are randomized into groups 1 to 5 using the allocation ratio 2:2:2:2:1. This is achieved by stratifying randomization on site (10 sites) and, within site, using blocking of size 9 with each block containing two occurrences of a given active group (1 to 4) and one occurrence of placebo (group 5) in random order. The assignment of group to any new eligible patient occurs through the eCRF in such a way that blinded staff will have access to the randomization date and number only. The randomization list is prepared and uploaded to the eCRF system by a statistician who remains in an unblinded role throughout the blinded part of the study.

2.6 Data pre-processing

The data processing chain from the raw data received from data management to End-of-Text documents contains steps to convert data from electronic case report form (eCRF) modules and external data sources, into datasets compliant with Clinical Data Interchange Standards Consortium (CDISC) standards. The first step of the process converts data into standardized CDISC Study Data Tabulation Model (SDTM) domains.

In the second step of the process, the SDTM domains are used to produce standardized CDISC Analysis Data Model (ADaM) datasets. In the third step, the table, listing, and figure (TLF) elements are produced from the ADaM datasets. In the final step, the TLF elements are collected and stored in End-of-Text (EOT) documents.

3 Analysis sets

In this section, the different analysis sets to be used for statistical analysis are presented. Each subject will be classified according to the definitions below at blinded data review meetings. The classification and related decisions will be made by the study team and documented in the minutes from the meeting. The Baby Immunogenicity Set (BIG) and Baby Per Protocol Set (BPP) refer to the babies born to study subjects.

All safety analyses will be performed on the Safety Analysis Set (SAF) and analysed according to the actual treatment received (treatment arms 1 to 5). All Immunological analyses will be performed on the Maternal Immunogenicity Set (MIG) and BIG sets. The primary immunological analysis (i.e., the immunogenicity results at delivery) will also be performed on the BPP set. These analyses will be based on randomised treatment.

3.1 Protocol deviations

Deviations from the protocol, as continuously tracked by investigator and sponsor, will be classified as ‘minor’ or ‘major’ on a case-by-case basis. The final classification of the deviations will be decided at the final Data Review Meeting prior to database lock.

All major protocol deviations will be summarised with frequency and percentage for each category of protocol deviation.

All protocol deviations, with classification minor/major, will be presented in a listing. Further protocol deviations might be identified during the final data review meeting, but likewise certain deviations might eventually be classified as non-deviations. These decisions will be documented in the minutes from the meeting. Note that the determination of analysis sets can be made based on (subject-level) information collected during the period from randomization until 72 hours after delivery.

3.2 Safety analysis set (SAF)

The safety analysis set (SAF) comprises all randomized **mothers** who receive at least one dose of the study vaccine or placebo.

3.3 Maternal Immunogenicity Set (MIG)

Maternal Immunogenicity Set (MIG) contains the subset of SAF (**mothers**) who receive at least one dose of the study vaccine or placebo and provide an evaluable sample for analysis on any day following first exposure to study vaccine.

3.4 Maternal Per Protocol Set (MPP)

Maternal Per Protocol Set (MPP) is the subset of MIG (**mothers**) who receive all doses of the study vaccine or placebo and provide evaluable samples for analysis on the day of the primary immunological endpoint and do not violate the protocol (no major protocol violation/deviation) up to and including the day of delivery.

3.5 Baby safety set (BSA)

Baby safety set (BSA) contains the **babies** born to mothers who have received at least one dose of the study vaccine or placebo (i.e., mothers who belong in the SAF). Note that the number of babies in the BSA could be smaller than the number of mothers in the SAF.

3.6 Baby Immunogenicity Set (BIG)

Baby Immunogenicity Set (BIG) contains the babies born to SAF mothers where the baby provides evaluable samples for analysis, either cord or venous blood, within 72 hours of birth. Note that there need not be a 1:1 correspondence between the MIG and BIG.

3.7 Baby Per Protocol Set (BPP)

Baby Per Protocol Set (BPP) contains the subset of BIG (babies) born to MPP mothers where the baby provides evaluable samples for analysis, either cord or venous blood within 72 hrs of birth.

Note that the BPP will be smaller or equal to the MPP (in size).

4 Statistical analyses and presentation of data

4.1 General considerations and summary of analyses

Summary tables presenting immunogenicity data (mothers and babies alike) as well as AEs including solicited injection site events and systemic AEs following the vaccinations will be presented a) pooled across all countries/sites and b) by geographical location South Africa / Europe (DK+UK).

All data collected from all sites will be sent to and analysed at Larix. Unless otherwise specified, all statistical tests will be performed using a two-sided test at a 5% significance level. Results from analyses will be presented with estimates, 95% confidence intervals (CIs) and p-values. For log-transformed analyses, which might be relevant for immunogenicity endpoints, the anti-log transformation will be applied before presentation. These transformed data will also be tabulated by geometric mean and coefficient of variation. Exposure to vaccinations and compliance with the vaccination schedule will be tabulated and listed.

Numerical/continuous data will be presented in summary tables by number of subjects, arithmetic mean (geometric mean and coefficient of variation [CV] where applicable), median, standard deviation (SD), minimum and maximum (or range). Categorical data will be presented by frequency and percent of subjects as well as number of events, where applicable. All data will be listed (see section 9, Layout of the outputs), and all endpoint data will be tabulated.

As there are more than one observation per subject (both mothers and babies) over time, time-dependent visualizations and, if possible, corresponding time-dependent statistical tests and modelling are carried out.

Prior and concomitant medication will be coded after WHO Drug Dictionary. Medical history and adverse events will be coded using the latest available version of MedDRA.

4.2 Data imputations

As the main principle, data will be analysed as collected and no imputation performed.

Adverse events

Missing causality, intensity, seriousness, and outcome of an adverse event (AE) will not be imputed in summary reporting.

Adverse events and concomitant medication dates

If the start date of an AE is incomplete, a full start date will be imputed following a ‘worst case’ logic favouring treatment emergency and length of AE duration. If the incomplete start date is un-ambiguously before date of first vaccination, the latest possible date compatible with the partial date, but before first vaccination, will be chosen. Otherwise, the earliest possible date compatible with the partial date, but after date of first vaccination will be chosen. So, for example:

Completely missing start date:

- the AE will be considered as concomitant/treatment emergent with the start date imputed as treatment start date.

If Month is missing:

- If the incomplete date is in the same year as day of first dosing, assign the treatment start date as the AE/medication start date.
- If this is not the case, assign January as the month and the 1.th of January as day/month if AE/medication day is also missing.

If Year is missing:

- Impute the year of first vaccination. If the imputed date is then after first vaccination date then retain it. Otherwise impute the date of first vaccination.

4.3 Subject Disposition

All randomised subjects will be accounted for. All post-randomisation discontinuations will be summarised by reason for discontinuation. The number and characteristics of subjects screened but not found eligible will be stated in the clinical study report, together with a summary of reasons and types of failures. A detailed listing of these subjects will be provided.

The number of subjects in each analysis set as defined below will be summarised with frequency and percentage in a subject disposition table.

4.4 Demographics, baseline characteristics and concomitant medications

4.4.1 Demographics data and medical history

Demographic data for mothers contain age at delivery, race, weight, height, BMI, gestational age at randomization. Demographic data for babies: height, weight, gestational age, and gender. Tabulations of these data are performed by treatment group.

- Medical history and concomitant illness will be summarised by SOC and PT for MedDRA version 23.1 or later. The table will display the total number of subjects with medical history, the percentage of subjects (%) with a reported medical history and the number of illnesses reported and will be presented by SOC sorted alphabetically and PT sorted in decreasing frequency of occurrence.
- Prior and concomitant medication will be tabulated separately and summarized by WHO Drug Dictionary terms (version WHODRUG Global C3 September 1, 2020, or later). The table will display the total number of subjects with medication, the percentage of subjects (%) with medication and the number of medications and will be presented by ATC level 4 sorted alphabetically and preferred names sorted in decreasing frequency of occurrence. Prior and concomitant medications are defined as follows:
  - Prior medication: Any medication episode initiated prior to the start of treatment (IMP)
  - Concomitant medication: Any medication episode initiated during the treatment period
- Viral serology – eligibility data regarding Human Immunodeficiency Viruses (HIV) and hepatitis B and C

4.4.2 Baseline data

With respect to IgG antibody, **for mothers**, baseline data are defined as the non-missing assessment before the first injection of the first IMP.

For general safety assessments (vital signs), baseline is defined as the pre-dose measurement on Day 0 (Visit 1). For laboratory assessments (haematology, chemistry, coagulation, and urinalysis) baseline is defined as the last measurement prior to the first IMP injection.

Change from baseline will be derived for all post-baseline timepoints as the difference between each post-baseline timepoint value and the baseline value. If either baseline or post-baseline values are missing, no change from baseline will be calculated. For variables with positive values, by definition, percent change from baseline will be derived as change from baseline divided by the baseline value and multiplied by 100.

Baseline assessments of physical examination, vital signs, and laboratory measurements will be presented as part of the Safety tables and listings.

4.5 Analysis of immunogenicity (primary endpoint)

The primary objective of the study will be assessed using the following endpoints, based on the cord blood from subjects in the BIG set:

A) IgG antibody concentrations specific to each of the four chosen AlpN proteins.

B) Proportion of subjects reaching AlpN-specific IgG concentrations at or above the following cut points: 0.1, 0.2, 0.5, 1, 2, 4 and 8 μg/mL.

The primary immunological endpoints will be defined as the values of the above parameters obtained in cord blood at the time of delivery. According to protocol, a missing or invalid cord blood sample can be replaced by a venous infant blood sample, provided this is taken within 72 hours from delivery.

The GMC and corresponding 95% CI for the IgG antibody concentrations will be estimated, by intervention group, assuming a normal distribution on the log-scale, the anti-log transformation will then be applied before presentation. The proportion of subject reaching the IgG antibody concentrations above the prespecified cut points will be reported by intervention group and 95% confidence intervals will be derived using the Wilson method. Additionally, the endpoints will be compared, as described below, between the 5 intervention groups presented in Table 1.

In terms of interpretation, comparison between groups 1, 2, 3 and 4 will form the main focus, with group 1 as the perceived standard, whereas groups 2 and 3 each represent useful practical alternatives that are expected to perform on a comparable level, and group 4 as representative for a sub-optimal, but still useful vaccination experience that would be likely to occur in practice.

Estimand: The ‘treatment-policy (ITT/effectiveness)’ estimand is considered for the primary objective. The estimand is based on data collected in all randomized BIG subjects regardless of the mother’s possible discontinuation of trial product or treatment adherence.

Missing data: imputation is not envisaged, and data will be analysed as collected.

The comparison will be conducted as a series of non-inferiority tests, for each choice of antigen (4) and cut-point (7) with two margins:

- for IgG concentrations: here a GMC ratio of 2/3 is considered adequate.
- for binary endpoints (proportion of subjects with antibody concentrations over prespecified thresholds): 15% points (0.15) on the absolute scale

The null hypothesis for each binary endpoint is:

$$H_0: P_{\text{cut c, group k, antigen w}} < P_{\text{cut c,group 1, antigen w}} - 0.15$$

$$k = 2, 3, 4;\ w = 1, 2, 3, 4;\ c = 0.1, 0.2, 0.5, 1, 2, 4, 8$$

$P_{\text{cut c, group k, antigen w}}$ is thus the proportion of subjects with antibody levels above cut-point c, for vaccination group k when considering the IgG concentration specific to antigen w.

The statistical alternative hypothesis is thus:

$$H_1: P_{\text{cut c, group k, antigen w}} >= P_{\text{cut c,group 1, antigen w}} - 0.15$$

If H_0 is rejected this indicates non-inferiority for one specific cut point and antigen.

The evaluation will be done by calculation of the unadjusted risk difference:

$(P_{\text{c, group k, w}} - P_{\text{c,group 1, w)}}$

with a two-sided 90% CI, corresponding to a one-sided test at the 5% significance level. The CI's will be approximative Newcombe-Wilson intervals. The H_0 is rejected if the CI is fully above the -15% point limit, and this therefore corresponds to a one-sided test at a 5% level.

The derivation of the unadjusted risk differences ($P_{\text{c, group k, w}} - P_{\text{c,group j, w)}}$, with corresponding two-sided 90% CIs, will be derived for all pairs 1 <= k, j <=4 and all antigens 1<= w <=4.

For the observed IgG concentrations, the comparison will be done with the same grouping, but using geometric mean concentrations. Here the H_0 can be expressed as:

$$H_0: GMC_{\text{group k, antigen w}} < 2/3 * GMC_{\text{group 1, antigen w}}$$

$$k = 2, 3, 4;\ w = 1, 2, 3, 4$$

The evaluation will be done by calculation of the GMCR (GMC ratio) with a two-sided multiplicative 90% CI, again corresponding to a one-sided test at the 5% significance level. The CI's will be based on log-normality. The H_0 is rejected if the CI is fully above the GMCR=2/3 limit and this therefore corresponds to a one-sided test at a 5% level.

The derivation of the GMCRs with corresponding two-sided 90% CIs, will be derived for all pairs 1 <= k, j <=4 and all antigens 1<= w <=4.

As a supplementary analysis, all groups (including placebo) are compared using Analysis of Variance (ANOVA) of the log-transformed values. No adjustment for multiplicity is done.

Due to the large number of performed tests, the non-inferiority procedures are considered of non-confirmatory nature and no control for multiplicity is applied. The expected power of many of the comparisons will be quite low, so only descriptive use of results will be considered.

The primary analyses are based on the BIG analysis set. As sensitivity analyses the primary analyses will be repeated on the BPP analysis set and will be repeated on the BIG set restricted to the babies with an evaluable cord blood sample. A further sensitivity analysis will be done on a further subset of the BPP, eliminating biologically implausible data. Examples of such biological implausible data are (non exhaustive list):

- Data from babies born to mothers with a high concentration of antibodies at delivery, where the baby blood at birth shows no or a very low concentration of antibodies, but who show a high concentration of antibodies at later timepoints
- Data from babies born to mothers with a high concentration of antibodies at delivery, where the baby blood shows no or a very low concentration of IgG antibodies, but where IgG1 is detected at the same timepoints, as part of an exploratory analysis

Setting of the elimination of biologically implausible data will be done after review of the initial immunogenicity data output.

4.6 Analysis of immunogenicity (secondary endpoints)

The following secondary immunogenicity endpoints will be evaluated by standard tabulation by vaccination group and relevant time-point(s):

Based on samples collected in the mother (MIG analysis setc):

- Concentrations of IgG antibodies specific to the 4 AlpN proteins in maternal blood, pre-dosing, 4 weeks after each vaccination dose and at delivery
- Relative to baseline (pre-dose) concentrations of IgG antibodies specific to the 4 AlpN proteins in maternal blood, pre-dosing, 4 weeks after each vaccination dose and at delivery

The proportions of mothers who achieve a concentration of IgG specific to the 4 AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at delivery

Based on samples collected in the mother (MIG analysis set) and in the baby (BIG analysis set), and as a sensitivity analysis based on subjects part of the BPP and MPP analysis sets. A further sensitivity analysis will be done on the BPP and MPP, in which biologically implausible data will be eliminated. Examples of such biological implausible data are (non exhaustive list):

- Data from babies born to mothers with a high concentration of antibodies at delivery, where the baby blood at birth shows no or a very low concentration of antibodies, but who show a high concentration of antibodies at later timepoints
- Data from babies born to mothers with a high concentration of antibodies at delivery, where the baby blood shows no or a very low concentration of IgG antibodies, but where IgG1 is detected at the same timepoints, as part of an exploratory analysis

Setting of the elimination of biologically implausible data will be done after review of the initial immunogenicity data output.

- The subject level ratios of antibody concentrations between maternal and cord blood at delivery. The ratio of interest is the antibody concentration measured in cord blood over the antibody concentration measured in maternal blood at delivery. The endpoint is derived for the individual mother-child pair.

Based on samples collected in the baby (BIG analysis set):

- Concentrations of IgG antibodies specific to the AlpN proteins in infant blood of each baby at 1 month and 3 months of age:
- The proportions of babies who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at 1 month and 3 months after birth will be calculated

For treatment groups 1 to 4, in a joint analysis, the maternal IgG concentrations from pre-dosing to delivery will be analysed using a log-normal model with repeated measurements within subject, vaccination group and visit as factors and a visit * group interaction.

An unstructured covariance structure will be implemented for repeated measurements. In case of estimation issues, an auto-regressive AR(1) covariance structure will be used instead to model the correlations within-subject. The Satterthwaite approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

Pseudo code related to the implementation of this model:

```
proc mixed data = IgG data;
  class subject group visit region;
  model change_log_titre = baseline  region group*visit  / ddfm=sat;
  repeated visit / subject=subject type=UN;
  lsmeans group*visit / diffs cl obsmargins;
run;
```

Here *change_log_titre* is the change from baseline in log(titre), *baseline* is the log(titre) at baseline and *visit* is the study Visit (i.e., 3, 5, 7, 8).

Least square mean estimates of change from baseline in log(titre) with 95% confidence intervals (CI) will be presented after applying the inverse transformation at each time-point for each treatment group.

Estimated group differences at Visit 7 and 8 (when vaccination schedule has been completed) between vaccination groups along with associated 95% confidence intervals and p-values will be presented.

Estimated least square means and associated 95% CI of change from baseline in log(titre) will be plotted over time by treatment group.

4.7 Analysis of safety (key secondary endpoint)

4.7.1 Adverse events

AEs relating to mothers (study subjects) will be coded using the latest available version of MedDRA. An overall summary table will be provided showing the number and percentage of subjects, within the SAF analysis set, with any:

- Treatment-emergent adverse events (TEAEs)
- Severe TEAEs
- Vaccine related TEAEs
- Vaccine related severe TEAEs
- Treatment-emergent SAE
- Treatment-emergent vaccine related SAEs
- TEAEs leading to withdrawal
- TEAEs with outcome death

The frequencies of the following key secondary safety endpoints will be tabulated in descriptive frequency tables:

- Treatment-emergent solicited injection site reactions
- Treatment-emergent solicited systemic AEs
- All treatment-emergent AEs
- For solicited events and reactions the summary tables will furthermore be presented by vaccination number/visit.

Treatment emergent AEs will be tabulated by system organ class and preferred term and treatment using the latest MedDRA coding.

All treatment emergent events will be listed. Non-treatment emergent events (if any) will be listed separately.

4.7.2 Adverse events and other safety assessments in babies.

AEs in babies will be analysed and presented similarly to AEs in mothers, described above.

With respect to the babies, the following set of safety information will likewise be tabulated for all relevant Visits (8, 9, 10, 11) in descriptive summary tables (BSA analysis set):

- Gestational age
- Weight

- Length
- Head circumference
- Apgar score at 1, 5 and 10 minutes
- Developmental milestones at 6 months of age

4.7.3 Safety laboratory assessments

Treatment groups are compared with respect to safety laboratory tests, urinalysis, and vital sign measurements, considering clinically significant results and evaluation of change from baseline, using descriptive statistics.

Absolute values and change from baseline in haematology and clinical biochemistry parameters will be summarized by visit and treatment group using descriptive statistics.

Frequency and percentage for categorical urinalysis data will be presented by visit and treatment group, when relevant.

Laboratory values will be flagged if outside the reference range.

A listing of abnormal values will be presented.

Descriptive statistics for vital signs parameters (systolic and diastolic blood pressure, heart rate, and body temperature) and weight will be presented in the same way as the laboratory parameters.

4.8 Analysis of weight of infant (exploratory endpoint)

Weight of the infant is not considered an endpoint in the protocol. It is however measured on four occasions and since weight of newborns is generally considered of medical importance weight will be made, comparing the 5 treatment groups (including group 5). The change-from-baseline (birth) in infant weight will be analyzed using a simple random effects model. Pseudo code related to the implementation of this model:

```
proc mixed data = weight data;
  class subject group visit region;
  model change_weight = birth_weight region group*visit / ddfm=sat;
    random intercept / subject=subject;
  lsmeans group*visit / diffs cl obsmargins;run;
```

Change_weight is the change from baseline in weightand *visit* is the study Visit (i.e., 9, 10, 11). Least square mean estimates of change from baseline in weight with 95% confidence intervals (CI) will be presented at each visit for each vaccination group. Estimated group differences at visit 11 between vaccination groups along with associated 95% confidence intervals and p-values will be presented. Estimated least square means and associated 95% CI of change from birth weight will be plotted over time, by vaccination group.

4.9 Analysis of immunogenicity (exploratory endpoints)

The exploratory immunogenicity analysis for this study will be described in a separate statistical analysis plan (SAP) under the responsibility of researchers in MinervaX AB, Sweden.

5 Centralized monitoring

Centralized monitoring will be performed regularly throughout the study. According to the general monitoring plan this activity will in particular cover assessment of:

- Recruitment rate, overall and per site.
- Vaccination compliance overall and per site (successful dosing, timing, and correct visit intervals).
- eDiary compliance, overall and per site.
- eDiary versus Adverse Events reporting consistency, solicited Adverse Events and Reactions.
- eDiary versus Adverse Events reporting consistency, unsolicited Adverse Events.
- Adverse Events that warrant temporary halt (study stopping rules), as per the protocol section 6.8.
- Serious Adverse Events, overall and per site.
- Reasons for not randomized/failed criteria.
- Reasons for withdrawal of individual subjects, overall and per site.
- Safety laboratory tests, outliers or clinically significant.
- Vital signs, outliers (including clinically significant and severe outliers).
- Adverse Events related to injection site reactions, overall and per site.
- Adverse Events frequencies (numbers of subjects with AE), overall and per site - Mothers.
- Adverse Events frequencies (numbers of subjects with AE), overall and per site - Babies.
- Adverse Events frequencies resulting in postponed dosing, overall and per site.
- Adverse Events frequencies resulting in withdrawal of study treatment, overall and per site.
- Adverse Events of special interest, overall and per site.
- Overdue visits (calculated from previous visit) where no data is present.
- Immunogenicity sampling compliance, overall and per site.

Occurrence of the following adverse events are followed in close to real time:

- SAE following vaccination for which the investigator estimates a causal relation
- Anaphylaxis or bronchospasm following vaccination that is considered at least possibly related to the vaccination
- Multiple occurrences of severe (grade 3) AEs considered possibly related to the vaccination

6 Interim analyses

There will be blinded, sponsor-internal safety reviews conducted on an ongoing basis as well as recurrent reviews by an unblinded DSMB. The function and responsibilities of the DSMB is documented in the DSMB Charter. The DSMB and the attached independent unblinded statistician and programmer will work in a setup completely separated from the blinded study team.

Unblinded analysis of selected endpoints up to (and including) Visit 8 will be performed based on cleaned data. This analysis (summaries and statistical analysis as described in section 4) will include the primary immunological endpoint for IgG antibodies specific to the AlpN proteins in cord blood, the key secondary safety endpoints in all study participants (maternal participants and babies), and the secondary immunological endpoint for IgG antibodies specific to the AlpN proteins in maternal blood. An overview of the considered objectives, endpoints, and relevant visits is given in Table 5 below.

This analysis will be conducted by an unblinded team within the CRO and sponsor. Separate teams within the CRO and the sponsor will remain blinded until the end of the study to ensure further study execution in a blinded manner. Investigators, and further site personal and study participants will remain blinded until the end of the study. Procedures to ensure that blinded and unblinded personnel remain in their roles are described in a ‘firewall’ charter, an extension of the general blinding plan.

As no hypotheses are tested repeatedly and no early stopping of the trial is envisioned, no multiplicity adjustments related to the early analysis are planned.

Table 5: endpoints directly relating to primary and secondary objectives evaluable after Visit 8 (delivery)		
Objective	Endpoint	Related visits
Primary objective	Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in cord blood from each baby: • The geometric mean antibody concentrations at birth will be calculated • The proportions of babies who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at birth will be calculated	Visit 8
Secondary objective: Safety	Mother: • Local and systemic reactogenicity and adverse events: • Solicited injection site reactions following the vaccinations • Solicited systemic adverse events following the vaccinations • All other adverse events following the vaccinations • Laboratory tests; urinalysis; vital signs (heart rate, blood pressure, oral body temperature); physical examinations	Visit 1 to Visit 8
	Baby: • Gestational age • Weight • Length • Head circumference • Apgar score at 1, 5 and 10 minutes • AEs	Visit 8
Secondary objectives: Immunogenicity	Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in <u>maternal blood:</u>	
	• The geometric mean antibody concentrations at delivery, and geometric mean concentration ratios relative to baseline will be calculated	Visit 1 and 8
	• The proportions of mothers who achieve a concentration of IgG specific to the AlpN proteins above 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL at delivery will be calculated	Visit 8
	• The geometric mean antibody concentrations at 4 weeks after each dose of vaccine/placebo and geometric mean concentration ratios relative to baseline will be calculated	Visit 1, 4, 6, and 7
	• The ratios of antibody concentrations between cord blood and maternal blood at delivery will be calculated	Visit 8

7 Deviations from protocol

- An exploratory analysis of weight of infant over time is added.
- Adverse events in babies are added as secondary safety endpoint(s).
- Central monitoring is described in some detail, but no specific analysis of monitoring data is defined.

8 Quality control

Programs used to derive the subject-level ADaM analysis dataset and the efficacy endpoints from the SDTM domains will be reviewed through parallel programming by an independent Statistical Programmer. Other ADaM datasets will be reviewed by code review. Furthermore, the programs involving the statistical analyses of primary and secondary efficacy endpoints will be reviewed using parallel programming by an independent statistician.

Other output programs will be reviewed by code review. All quality control activities for individual programs will be carried out in compliance with Standard Operating Procedure (SOP) 703, Programming of Single Use SAS Programs. All review findings and their follow-up will be documented in a Program Overview Form.

9 Layout of output

Following the International Council on Harmonization: Guideline for Industry Structure and Content of Clinical Study Reports (ICH-E3), a structured numbering will apply for the EOT documents. RTF files will be used as the format for single output files with font type as Times New Roman of size 9. PNG files will be used for graphics, and Microsoft Office Word 2010 (or later) files (DOCX) files will be used as the format for TLF collections (EOT documents).

Data analysis and presentation will be performed by SAS Viya version 03-05 or later.

The sponsor's name (MinervaX), protocol number (MVX0004), SAS program and output name and run date will appear at the bottom right in a footnote. The header of the EOT document will include date of collection and status (draft/final).

10 Tables, listings and figures

A document containing key table shells will be provided separately together with a suggested detailed list of EOT outputs (TLFs).

11 Change log

Version	Effective date	Reason for revision
Draft v. 0.1	29-Apr-2022	New document
Final 1.0	07-Jun-2022	First final version
Final 2.0	23-Sep-2022	Second final version following FDA review
Final 3.0	11-May-2023	Addition of interim analysis and various clarifications
Final 4.0	30-Aug-2023	Addition of sensitivity analysis excluding biological implausible samples and various clarifications

12 References

[1] BS-NN/NN2 Study Protocol, Study ID: MVX0004, Date 14-Apr-2023, Version 5.0.

[2] de Gier B, van Kassel MN, Sanders EAM, van de Beek D, Hahné SJM, et al. (2019) Disease burden of neonatal invasive Group B *Streptococcus* infection in the Netherlands. PLOS ONE 14(5): e0216749. https://doi.org/10.1371/journal.pone.0216749.

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