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Statistical analysis plan

A multi-Centre, randomised, placebo controlled, double-blind, parallel group study to evaluate the safety, tolerability and immunogenicity of two doses of Group B Streptococcus vaccine (GBS-NN/NN2) in women who are pregnant and living with HIV and women who are pregnant and do not have HIV.

FINAL v1.0

Sponsor:	**MinervaX**
Contract research organisation:	**Signifikans Aps**
Sponsor protocol number:	**MVX-0005_UG/ MVX0005_ZA**
Investigational product name:	**GBS-NN/NN2**
Development phase:	**Phase II**

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List of abbreviations and definition of terms

ADaM	Analysis data model
AE	Adverse event
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
CMO	Chief Medical Officer
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

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[redacted]	[redacted]
PD	Pharmacodynamic
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

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1 Introduction

Group B Streptococcus disease and vaccine

Reference: Study protocols [1] and [2].

Streptococcus agalactiae, also referred to as Lancefield's group B Streptococcus (GBS), is a Gram-positive diplococcus representing one of the most common causes of life-threatening invasive bacterial infections in neonates and young infants. Infections can result in neonatal sepsis, pneumonia and meningitis, and is associated with significant mortality and morbidity, including long-term neuro-developmental. GBS is also associated with disease in adults, particularly in pregnant woman, elderly and adults with underlying condition such as HIV, cancer, cirrhosis and diabetes. GBS had emerged as the predominant disease in neonates and young infants, who develop invasive GBS disease, as a result of invasion of GBS across epithelial cells . HIV-exposed infants are at a higher risk of developing invasive GBS disease.

The global incidence per 1 000 live births of invasive GBS disease in infants <90 days of age is estimated to be 0.53 (95% confidence interval (CI) 0.44 - 0.62) with a case fatality ratio of 9.6%. South Africa and Uganda have high incidences of invasive neonatal GBS infection, with high associated fatality rates. For those that survive there is a high incidence of significant neurological impairment. The high incidence in these two countries might be due to suboptimal implementation of intrapartum antibiotic prophylaxis (IAP), which is the current treatment. The increased susceptibility to invasive GBS disease in infants born to HIV-infected women is thought to be due to lower maternal protective GBS capsular antibody concentrations and the inefficient transplacental transfer thereof.

Currently, South Africa, Uganda and other low-to-middle-income counties, practise the less successful risk-based approach to prevent invasive disease, i.e. IAP is only provided to mothers in labour with risk factors such as maternal fever, prolonged rupture of membranes or prematurity. This strategy is also failing in low-to-middle-income countries because risk factors do not identify all women who are at risk of transmitting GBS to their baby. Furthermore, healthcare workers may fail to recognise risk factors, and may not provide IAP in busy obstetric units. Penicillin is still drug of choice for infants who require treatment for invasive GBS disease. In light of the provision of IAP being costly and logistically difficult to implement; maternal GBS vaccination is a promising strategy.

The maternal GBS-NN/NN2 vaccine is targeting Alp1, Alp2, AlpC, and Rib antibodies through two fusion proteins, GBS-NN and GBS-NN2, each containing two of the N-terminal domains mentioned above. The focus of this protein vaccine study is on the antibody concentrations in the blood of pregnant woman living with and without HIV,their infants and the transfer rate of antibodies across the placenta from mother to baby.

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1.1 Overview

1.1.1 Study Design

This is a Phase II, randomised, placebo controlled, double-blind, parallel group, multi-centre study. There will be 4 groups as described in Table 1.

Table 1. Overview assignment to groups

Group	No. Subjects	HIV	Treatment
1	80	Yes	Vaccine
2	80	No	Vaccine
3	20	Yes	Placebo
4	20	No	Placebo

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1.1.2 Endpoints

Table 2. Overview of primary safety endpoints

Endpoint	Mother/ baby	Time points	Details	Specification	From
Primary safety	Mother	From vaccination up to delivery/birth	Local and systemic reactogenicity	Injection site redness, bruising, swelling, itching, pain, and tenderness; headache, sore throat, “flu-like” symptoms, muscle aches, fever in the 72 hours post dose	
			Adverse events		
			Laboratory tests;		
			Dipstick urinalysis		
			Vital signs		
			Physical examination		
Primary safety	New-born baby	At birth	Gestational age at birth	based on ultrasound, date of last menstrual period, fundal height, as per the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) guidelines	
			Weight		
			Length		
			Head circumference		
			Apgar score at 1, 5 and 10 minutes		
			Infant Adverse events from birth to first visit after birth (Visit 6, 28±4 days post-delivery)		

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Table 3. Overview of primary immunogenicity endpoints

Endpoint	Mother/ New-born baby	Timepoints	Details	Specification	From
Primary immunogenicity	The subject level ratio of IgG antibody concentrations between mother and baby, Transfer rate (%)	At birth	The transfer rate is concentration in baby at birth/concentration in mother at delivery expressed as a percentage.	For each IgG specific to Alp1, Alp2, AlpC. and Rib, the transfer rate. E.g. for Alp1; transfer rate= (Alp1 in baby at birth)/(Alp1 in Mother at delivery)	Lab data

Table 4. Overview of secondary safety endpoints

Endpoint	Mother/ New-born baby	Time points	Details	Specification
Secondary safety	Mother	From delivery to 12 months post-delivery (as assessed at 6 and 12 months post delivery)	Adverse events	SAEs, adverse events of special interest (potential immunotoxicity, e.g. development of auto immune diseases) and related concomitant medication
Secondary safety	Baby	From delivery to 12 months post-delivery (as assessed at 6 and 12 post delivery)	Adverse events	Adverse events
			Developmental milestones	As assessed using ages and stages questionnaires

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Table 5. Overview of secondary immunogenicity endpoints

Endpoint	Mother/ New-born baby	Time points	Details	Specification
Secondary immunogenicity	Mother	• 4 weeks post first (pre-second injection) • 4 weeks post second injection.	Geometric mean antibody concentration in µg/ml at 4 weeks post first (pre-second injection) and 4 weeks post second injection.	IgG antibodies specific to Alp1, Alp2, AlpC and Rib
		• 6 months post delivery	Geometric mean antibody concentration in µg/ml in maternal blood 6 months post delivery	
	Infant	• 1-, 2-, and 3-months post birth	Geometric mean antibody concentration in µg/ml in infant blood 1-, 2-, and 3-months post delivery	
	Mother and infant	• At delivery.	Geometric mean antibody concentration in µg/ml of cord (or venous blood within 48 hours of birth) and maternal blood at delivery.	IgG antibodies specific to Alp1, Alp2, AlpC and Rib
	Mother	• 4 weeks post first (pre-second injection) • 4 weeks post second injection.	Geometric mean fold increase of antibody concentration in maternal blood from baseline to 4 weeks post first (pre-second injection) and 4 weeks post second injection.	IgG antibodies specific to Alp1, Alp2, AlpC and Rib
	Mother	• Baseline to delivery.	Geometric mean fold increase of antibody concentration in maternal blood from baseline to delivery.	IgG antibodies specific to Alp1, Alp2, AlpC and Rib
	Mother and infant	• At delivery.	Proportion of mothers and new-born babies achieving vaccine specific IgG antibody concentrations, in maternal and cord blood samples respectively, above pre-specified arbitrary thresholds at delivery (these will be 0.5, 1, 2 µg/ml).	IgG antibodies specific to Alp1, Alp2, AlpC and Rib

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1.1.3 Analysis Populations

Table 6. Overview of analysis data sets

Abbreviation	Analysis population	Description
SAF	Safety Analysis Set (SAF)	All randomized mothers who receive at least one dose of the study vaccine or placebo.
BSA	Baby safety set (BSA)	Babies from SAF mothers
MIG	Maternal Immunogenicity Set (MIG)	Mothers in SAF who provide at least one evaluable sample for analysis on any day following first exposure to study vaccine.
BIG	Baby Immunogenicity Set (BIG)	The Babies born to mothers in the SAF set and for who an evaluable cord blood or venous blood sample within 48 hours of birth is collected.
MPP	Maternal Per Protocol Set (MPP)	MIG with evaluable samples for analysis on the day of the primary immunological endpoint (day of delivery) and do not violate the protocol (no major protocol violation/deviation).
BPP	Baby Per Protocol Set (BPP)	Babies born to mothers in the MPP set with evaluable samples for analysis (cord or venous blood within 48 hrs of birth)

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1.2 Study objectives and endpoints

In this section, objectives of the study together with their corresponding endpoints are presented as written in Clinical Study Protocols [1] and [2].

1.2.1 Objectives

1.2.1.1 Primary objective

There are two primary objectives, and they are assessing safety, tolerability, and immunological effect of GBS-NN/NN2:

Safety and tolerability:

To evaluate the safety and tolerability of the GBS-NN/NN2 vaccine in women living with HIV and mothers without HIV and their new-born babies from vaccination up to delivery/birth.

Immunological:

To compare the transfer rate of vaccine specific immunoglobulin G (IgG) antibody concentrations **from the mother to the baby** at birth in women living with HIV with the transfer rate in women without HIV. This endpoint was used to determine the sample size calculation.

1.2.1.2 Secondary objective: Safety

The secondary objectives are as follows:

Safety and Tolerability:

The safety and tolerability of the GBS-NN/NN2 vaccine in the mother and baby over the first 12 months **post-partum**, as assessed at 6 and 12 months of age.

Immunological:

The secondary immunological objectives are:

- To compare IgG antibody responses, specific to Rib, Alp1, Alp2 and AlpC, induced by the first and second vaccine doses over time in pregnant women living with HIV and pregnant women without HIV.
- To determine the concentrations of IgG antibodies specific to Rib, Alp1, Alp2 and AlpC in cord blood at delivery in babies born to women with and without HIV.
- To evaluate the concentration of IgG antibodies specific to Rib, Alp1, Alp2 and AlpC up to 6 months post-delivery in the mother and 3 months post-delivery in the baby in women with and without HIV.

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- To evaluate the vaccine specific IgG concentration time profile over time, in the baby over the first 3 months of life and compare this between babies born of mothers living with and without HIV.

1.2.1.3 Exploratory objectives

The exploratory objectives are as follows:

- [redacted]
- [redacted]

1.2.2 Endpoints

1.2.2.1 Primary endpoints

Safety:

The following endpoints **in the mother** will be evaluated to support this objective: local (injection site redness, bruising, swelling, itching, pain, and tenderness) and systemic reactogenicity (headache, sore throat, "flu-like" symptoms, muscle aches, fever in the 72 hours post dose); adverse events; laboratory tests; dipstick urinalysis; vital signs; physical examination.

Admissions to hospital for a normal vaginal delivery (NVD) or following an elective Caesarean section leading to a healthy, term birth will not be deemed a serious adverse event. If a participant requires an emergency caesarean section, the reason for the Emergency Lower Segment Caesarean Section (LSCS) will be reported as a SAE.

In the new-born baby: gestational age at birth (based on ultrasound, date of last menstrual period and fundal height as per the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) guidelines), weight, length, head circumference, Apgar score at 1, 5 and, if available, at 10 minutes.

The data for the primary endpoint will be the data collected at the assessments conducted at delivery.

Immunological:

The IgG antibody concentrations specific to Rib, Alp1, Alp2 and AlpC in individual maternal blood and cord blood at birth. For each of the specific IgG antibody concentrations. the transfer rate is defined as concentration in baby at birth/concentration in mother at delivery expressed as a percentage:

$$\frac{IgG\ concentration\ in\ cord-blood}{IgG\ concentration\ in\ maternal\ blood\ at\ delivery} \times 100 = Transfer\ rate\ (\%)$$

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1.2.2.2 Secondary endpoints

Safety:

Mothers and babies will be followed up for 12 months post-delivery, mothers will be assessed for significant adverse reactions with specific interest in potential immunotoxicity e.g. development of auto immune diseases.

Developmental milestones of the babies will be assessed at 6- and 12-months using the ages and stages questionnaire, as per Appendices.

Immunogenicity:

The following endpoints will be evaluated, by group and time-point, to support the immunological secondary objectives:

- Geometric mean antibody concentration in µg/ml at 4 weeks post first (pre-second injection) and 4 weeks post second injection.
- Geometric mean antibody concentration in µg/ml in maternal blood 6 months post-delivery (added in SAP, not part of Protocol)
- Geometric mean antibody concentration in µg/ml in infant blood 1, 2, and 3 months post-delivery (added in SAP, not part of Protocol)
- Geometric mean antibody concentration in µg/ml of cord (or new-born blood within 48 hours of birth) and maternal blood at delivery.
- Geometric mean fold increase of antibody concentration in µg/ml in maternal blood at 4 weeks post first (pre-second injection) and 4 weeks post second injection.
- Geometric mean fold increase of antibody concentration in µg/ml in maternal blood from baseline to delivery.
- Proportion of mothers and new-born babies achieving vaccine specific IgG antibody concentrations, in maternal and cord blood samples respectively, above pre-specified arbitrary thresholds at delivery (these will be 0.5, 1, 2 µg/ml).

1.2.2.3 Exploratory endpoints

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

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2 Study design

This is a Phase II, randomised, placebo controlled, double-blind, parallel group, multi-centre study. There will be 4 groups, two groups of 80 participants to receive the potential vaccine and two groups of 20 participants to receive placebo.

Group 1: 80 women who are pregnant and living **with HIV**, who will receive two injections of GBS-NN/NN2. Each injection will contain 50 µg of GBS-NN and 50 µg of GBS-NN2.

Group 2: 80 women who are pregnant and do **not have HIV** who will receive two injections of GBS-NN/NN2. Each injection will contain 50 µg of GBS-NN and 50 µg of GBS-NN2.

Group 3: 20 women who are pregnant and living **with HIV** who will receive two injections of placebo.

Group 4: 20 women who are pregnant and **do not have HIV** who will receive two injections of placebo.

Participants will be screened at 24 to 28 weeks gestation, Day -14 to day -1. The groups will be dosed in parallel; the first dose of vaccine or placebo will be administered at Day 0 and the second dose will be administered Day 28±2 days after the first dose.

For the analysis of the immune responses the placebo groups will be combined. For safety, the placebo groups will be analysed separately and combined for comparison with the potential vaccine groups.

2.1 Randomization

An IBM central randomization schedule was generated on a balanced basis with a randomization ratio of 4:4:1:1. (80 pregnant women living with HIV to receive GBS-NN/NN2; 80 pregnant women who do not have HIV to receive GBS-NN/NN2); 20 pregnant women who are living with HIV to receive placebo; 20 pregnant women who do not have HIV to receive placebo). Eligible participants were randomised using a computerized IBM central randomisation system. Additionally, 50% of babies were randomised to have a PD sample taken at 2 months and the other 50% at 3 months.

2.2 Study visits and assessments

Visits and assessments are performed as presented in flowcharts (Table 7 and Table 8) below, for mothers and babies. A description of individual study visits can be found in Clinical Study Protocol [1] and [2].

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Table 7. Schedule of Assessments for Mothers

	Screening Period	Treatment and Follow-up Period									
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Assessment	Day -14 to Day -1 24 to 28 Weeks GA	Day 0 26 to 30 weeks GA	Day 7 to Day 10	Day 28 ±2	Day 56 ±2	Delivery	28±4 days post delivery	56±6 days post delivery	84±6 days post delivery	182±8 Days post delivery	365±8 Days post delivery
Informed Consent	X										
Inclusion/ Exclusion Criteria	X										
Demography	X										
Medical History	X										
Physical Examination	X	X		X			X			X	
Height, Weight, BMI,MUAC	X						X			X	
Vital signs[a]	X	X[b]	X	X[b]	X	X	X	X	X	X	
Urinalysis	X	X		X							
Ultrasound[h]	X										
Safety laboratory tests[d]	X			X	X	X[l]					
Hep B and Hep C	X										
Rapid HIV Test	X[f]					X[i]					
CD4 count	X[e]										
HIV viral load	X[e]										

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	Screening Period	Treatment and Follow-up Period									
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Assessment	Day -14 to Day -1 24 to 28 Weeks GA	Day 0 26 to 30 weeks GA	Day 7 to Day 10	Day 28 ±2	Day 56 ±2	Delivery	28±4 days post delivery	56±6 days post delivery	84±6 days post delivery	182±8 Days post delivery	365±8 Days post delivery
Review of participant eligibility		X									
Randomisation		X									
Administration Investigational vaccine		X		X							
PD blood sample – antibody response		X		X	X	X				X	
Diary card		X	X[j]	X	X[j]	X					
Assessment of injection site[c]		X	X	X	X						
Urine pregnancy test											X[g]
AE check	X							X[k]			X[k]
Prescription Concomitant medication check	X						X				X[k]

Footnotes

a. Heart rate, blood pressure and axillary temperature.

b. Vital signs at dosing Visit will be recorded pre-dose and at 30min post-dose.

c. Photographs may be taken of injection site reactions as required.

d. Haematology (Red blood cell count, Haemoglobin, Haematocrit, Platelet count, White blood cell count with absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) counts) and Biochemistry (Sodium, Potassium, Chloride, Bicarbonate, 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)

e. Only if participant is HIV positive

f. Only participants not known to be HIV positive

g. Any participant found to be pregnant at the end of the study will be followed up to delivery

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h. Ultrasound for assessment of gestational age, confirmation of singleton pregnancy and no detectable congenital abnormalities

i. Standard of Care test

j Review of diary only

k. SAEs, AEs of special interest and related con-meds

l. Safety laboratory tests collected if delivery before V4

Table 8. Schedule of assessments for Babies

	Visit 5	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
Assessment	Delivery	28±4 days post delivery	56±6 days post delivery	84±6 days post delivery	182±8 Days post delivery	365±8 Days post delivery
Demography[a]	X					
Gestational History	X					
Physical Examination	X	X	X			
Head Circumference	X	X	X			
Length	X	X				
Weight	X	X	X	X	X	
Apgar Score[b]	X[b]					
Vital signsc	X	X	X	X	X	
HIV Status	X[g]	X[g]	X[g]	X[g]		
Developmental milestones	X[f]	X[f]				
PD blood sample – antibody concentration	X[d]	X[e]	X[e,h]	X[e,h]		
AE check	X					
Con med check	X					

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

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d. Cord blood or Infant blood (heel prick or venous sample).

e. Heel prick or venous sample.

f. Developmental milestone scoring (Ages and Stages)

g. Record result of routine standard of care HIV serology assessment for the baby, if done as part of standard of care, in the eCRF if not recorded previously or if new results are available

h 50% babies at 2 months and the other 50% at 3 months. Only 3 samples total per baby

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2.3 Presentation of data

Below, a short overview of important variables used for presentation is shown. These comprise:

- Categorization variables
- Information repeatedly recorded within each subject
- Outcomes: i.e. response/dependent variables for analysis
- Occurrence data

Data are required for both mothers and babies.

2.3.1 Categorization:

- Country: South Africa and Uganda
- Sites (within each country): University of the Witwatersrand, Johannesburg, South Africa (sites RMPRU/Wits VIDA Research Unit Clinic and Wits) and MUJHU Research Collaboration/MUJHU Care Ltd, Uganda
- Groups:
    - G1 (HIV, active)
    - G2 (no HIV, active)
    - G3 (HIV, placebo)
    - G4 (no HIV, placebo)
    - All active (G1 and G2)
    - All placebo (G3 and G4)
- Target: Maternal, Cord
- Demographical variables for mothers: age of mother at screening, race, height, weight, BMI, gestational age at delivery
- Demographical variables for babies: age of mother at screening, height, weight, gender, gestational age
- Earlier occurrence of disease/infection caused by GBS bacteria (e.g., pneumonia, meningitis and/or sepsis), number of children born and medical history in general.

2.3.2 Repeated measurements/sampling

- Safety blood (serum biochemistry and haematology) for mothers, urine analysis, vital signs and physical examination for mothers and babies.

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2.3.3 Outcome variables

- The concentration of IgG antibodies specific to the 4 AlpN antigens (Alp1, Alp2, AlpC, Rib)
- [redacted]

2.3.4 Occurrence variables

- Adverse events / injection site reactions / adverse events of special interest
- Concomitant medication (CM)

2.4 Determination of sample size

2.4.1 Sample size justification

The power calculation will be based on the paper by Heyderman 2016[1], [2]: in which, the average standard deviation in the log transformed placental transfer ratios between patients was 0.96.

The sample sizes were calculated on the conservative assumption that only 60 participants per group would be enrolled, that there would be a 15% dropout rate, and that 80% of women would deliver infants that are at 37 weeks or more of gestation or weighed 2500 g or more at birth. Thus, a sample size of 40 per group would give approximately 95% power to detect an 8% difference in placental transfer rates between any two study groups.

2.5 Blinding

Blinding will be managed by the IBM system and will be explained in Section 10.2 of Clinical Study Protocols [1] and [2].

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.

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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 the database release meeting. The classification and related decisions will be made by the study team and documented in the minutes from the meeting. The Baby safety set (BSA), Baby Immunogenicity Set (BIG), and Baby Per Protocol Set (BPP) refer to the babies born to study subjects.

The Primary and Secondary Safety analyses will be performed on the safety analysis (SAF) set. The Primary and Secondary Immunological analyses will be performed on the maternal immunogenicity (MIG) and baby immunogenicity (BIG) sets. As a sensitivity analysis, the "primary" immunological analysis (i.e. the transfer rate at delivery) will also be repeated on the maternal per protocol (MPP) and baby per protocol (BPP) sets. Furthermore, additional immunological analyses might be performed eliminating datapoints with biological non plausible data (immunogenicity data). These additional analyses will be performed for cord blood related analyses, eliminating subjects for whom the immunogenicity results in the baby at V6 are ≥ 5-fold higher than the results in the cord blood for this baby (V5), and remain higher than cord blood at later timepoints.

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 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 Data Review Meeting.

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3.2 Safety Analysis Set (SAF)

All randomized mothers who receive at least one dose of the study vaccine or placebo.

3.3 Baby safety set (BSA)

The 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 to the SAF).

3.4 Maternal Immunogenicity Set (MIG)

Mothers in SAF who provide at least one evaluable sample for analysis on any day following first exposure to study vaccine.

3.5 Baby Immunogenicity Set (BIG)

The Babies born to mothers in the SAF set and for who an evaluable cord blood or venous blood sample taken within 48 hours of birth is collected.

3.6 Maternal Per Protocol Set (MPP)

The subset of mothers part of the MIG set who receive both doses of the study vaccine or placebo and provide evaluable samples for analysis on the day of the primary immunological endpoint (day of delivery) and do not violate the protocol (no major protocol violation/deviation).

3.7 Baby Per Protocol Set (BPP)

All babies with evaluable samples for analysis (cord or venous blood within 48 hrs of birth) born to mothers in the MPP set.

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4 Statistical analyses and presentation of data

4.1 General considerations and summary of analyses

The following data (safety, immunogenicity and exploratory endpoints) will be described according to visits and vaccine dose groups, if relevant:

Mother:

- Demographic and baseline data
- Safety data including:
  - Vital signs (heart rate, blood pressure and body temperature)
  - Safety laboratory tests (haematology, biochemistry)
  - Adverse events
  - Physical examinations
  - Assessment results of the injection site (local reactogenicity) and systemic reactogenicity using scale variables
- Pharmacodynamic blood sample results (antibody response)

Baby:

- Demographic and baseline data
- Apgar scores at 1, 5 and 10 minutes
- Gestational age
- Head circumference, weight and length
- Type of delivery
- Pharmacodynamic blood sample results (antibody response)
- Adverse events

For the analysis of the immune responses and safety, the placebo groups will be combined.

Data will be presented a) pooled across all countries/sites and b) by country (ZA/UG).

All data collected from all sites will be sent to and analysed at Signifikans Aps. 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 when relevant. For log-transformed analyses, e.g., the analyses of the antibody concentration related endpoints, the anti-log transformation will be applied before presentation. Subjects whose antibody concentrations are below the cut-off of the assay will be given a value of half the cut-off for the purpose of GMC

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calculation (i.e., if the concentration value is reported as "<X", X/2 will be used). 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 Layout of outputLayout of the output), and all endpoint data will be tabulated.

4.1.1 Safety and tolerability

The safety data will be summarised using number of subjects, observed number of events, event rates and corresponding 95% confidence intervals.

4.1.2 Immunogenicity

For the analyses, the immunological data will be performed on the log scale. The results will be reported as geometric means (ratios) and the corresponding geometric confidence intervals.

4.2 Listings and descriptive statistics

All observed and derived parameters, endpoints, as well as population characteristics, will be listed and described using summary statistics. All listings will include repeated and unscheduled measurements.

Unless otherwise specified, descriptive statistics for quantitative parameters will be provided using number of observations (N), arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum. For the immunogenicity endpoints, the data will be analysed on the log transformed values, before presentation of the results the anti-log transformation will be applied and the geometric mean and confidence interval will be reported.

4.3 Data imputations

As the attrition rate, i.e., the rate at which the subjects leave the study, is most likely very low, data will be analysed as collected. More details about imputation when addressing each objective are given in the following sections.

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

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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 1st 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.

4.4 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 will be summarised with frequency and percentage in a subject disposition table.

4.5 Demographics, baseline characteristics and concomitant medications

4.5.1 Demographics data and medical history

Demographic data for mothers contain age at screening, race, weight, height, BMI, pregnancy length. Demographic data for babies contain age of mother at screening, race, height, weight, gestational age, and gender. Tabulations of these data are performed by group.

- Medical history and concomitant illness will be summarised by SOC and PT for MedDRA version 23.1. 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

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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 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

4.5.2 Baseline data

With respect to IgG antibody, **for mothers**, baseline data are defined as the last 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.

4.6 Analysis of Primary Safety endpoints (primary endpoints)

The main safety objective of the study will be to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine in women living with HIV and mothers without HIV and their new-born babies from vaccination up to delivery/birth.

The following safety endpoints will be evaluated to support this objective:

Mother: local (injection site redness, bruising, swelling, itching, pain, and tenderness) and systemic reactogenicity (headache, sore throat, “flu-like” symptoms, muscle aches, fever in the 72 hours post dose); adverse events; laboratory tests; dipstick urinalysis; vital signs; physical examination.

New-born baby: gestational age at birth (based on ultrasound, date of last menstrual period, fundal height, as per the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) guidelines); weight; length; head circumference; Apgar score at 1, 5 and 10 minutes (if available); adverse events.

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4.6.1 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 event (TEAE)
- Severe TEAE
- Vaccine related TEAE
- Vaccine related severe TEAE
- Treatment-emergent SAE
- Treatment-emergent vaccine related SAE
- TEAE leading to withdrawal
- TEAE with outcome death

The frequencies of the following 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 be presented by visit and days since vaccination

Treatment emergent AEs will be tabulated by system organ class and preferred term and treatment using MedDRA Version 23.1 coding.

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

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

4.6.2 Safety laboratory assessments, urinalysis and vital signs

The groups will be 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 group using descriptive statistics.

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

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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.

4.7 Analysis of Immunogenicity (primary endpoints)

The primary objective of the study will be assessed using the following endpoints:

The subject level ratio of IgG antibody concentrations, specific to the 4 AlpN proteins (Rib, Alp1, Alp2, AlpC) in cord blood[1] over maternal blood at birth.

$$\frac{IgG\ concentration\ in\ cord-blood}{IgG\ concentration\ in\ maternal\ blood\ at\ delivery} \times 100 = Transfer\ rate\ (\%)$$

The primary endpoint will be evaluated by standard tabulation by group (group 1, group 2, and group 3 and 4 combined) and will be analysed by means of ANOVAs on the log transformed ratio data. The ANOVA model will be adjusted for site and pairwise comparisons will be performed on all the observed means. The resulting geometric means and geometric confidence intervals will be reported overall and by site.

The primary analysis is based on the MIG and BIG analysis sets. As sensitivity analyses the primary analyses will be repeated based on the BPP and MPP analysis set and will be repeated on the BIG and MIG set restricted to the babies with an evaluable cord blood sample.

An additional analysis of the primary objective might be performed eliminating datapoints from subjects with biological non plausible data. This additional analysis would be performed in case for at least one subject immunogenicity results in the baby at V6 are ≥ 5-fold higher than the results in the cord blood for this baby (V5) and remain higher than cord blood at later timepoints.

4.8 Analysis of Secondary Safety endpoints (Secondary endpoints)

Safety: Mothers and babies will be followed up for 12 months post-delivery, mothers will be assessed for significant adverse reactions with specific interest in potential immunotoxicity e.g. development of auto immune diseases.

The statistical analysis will be performed as for the analysis on the primary safety endpoint.

Developmental milestones of the babies will be assessed at 6- and 12-months using ages and stages questionnaire.

[1] Or a venous infant blood sample collected within 48h of birth in case a cord blood sample was not obtained.

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4.8.1 Ages and Stages Questionnaires (ASQ-3)

The Ages and Stages Questionnaire (ASQ-3) [3] is a screening tool used to assess the developmental progress of infants and young children in five key areas: communication, gross motor skills, fine motor skills, problem-solving, and personal-social skills. The analysis of ASQ-3 data involves several steps, including scoring and interpretation. Here's a general outline of the analysis process:

Scoring: Each item is scored as "10" if the child successfully completes the task, "5" if the child partially completes the task, or "0" if the child does not complete the task.

Domain Scores: Sum the item scores within each domain (communication, gross motor, fine motor, problem-solving, and personal-social) to obtain domain scores.

The ASQ-3 manual provides cutoff values to determine whether a child's performance falls within typical development or requires further evaluation.

Total Score: Sum all domain scores to obtain the child's total score. The total score can provide an overall measure of the child's development.

ASQ-3 will be tabulated for each domain and the total score will be summarized using descriptive statistics and will be presented by group. These analyses will be repeated for each of the relevant visits (Visit 5 and Visit 6).

4.9 Analysis of Immunogenicity (Secondary endpoints)

The following endpoints will be evaluated, by group (group 1, group 2, and group 3 and 4 combined) and time-point, to support the secondary immunogenicity objectives:

Based on samples collected in the mother (MIG set):

- Geometric mean antibody concentration in μg/ml at 4 weeks post first (pre-second injection) and 4 weeks post second injection.
- Geometric mean antibody concentration in μg/ml in maternal blood at delivery.
- Geometric mean antibody concentration in maternal blood in μg/ml 6 months post-delivery
- Geometric mean fold increase of antibody concentration in maternal blood from baseline to 4 weeks post first (pre-second injection) and 4 weeks post second injection.
- Geometric mean fold increase of antibody concentration in maternal blood from baseline to delivery.
- Proportion of mothers achieving vaccine specific IgG antibody concentrations above pre-specified arbitrary thresholds at delivery (these will be 0.5, 1, 2 μg/ml).

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

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- Geometric mean antibody concentration in μg/ml in infant blood 1, 2, and 3 months post-delivery
- Geometric mean antibody concentration in μg/ml of cord (or venous blood within 48 hours of birth) and maternal blood at delivery.
- Proportion of new-born babies achieving vaccine specific IgG antibody concentrations, in cord blood samples, above pre-specified arbitrary thresholds at delivery (these will be 0.5, 1, 2 μg/ml).

All geometric mean concentrations and geometric mean changes will be calculated by assuming a normal distribution of the antibody concentrations and the difference in antibody concentrations, respectively. The anti-log transformation will be applied before presentation of the results. The 95% CI of the proportions will be derived using the Wilson score method.

For the babies in the BIG set the vaccine specific IgG concentration time profile will be modelled using a mixed effects model. The change in $\log_{10}$-transformed IgG concentrations from Visits 5, 6, 7, and 8 will be analysed using a log-normal model with repeated measurements within subject, group and visit as factors, $\log_{10}$-transformed IgG concentrations at delivery as covariate, and a visit * group interaction.

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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 treatment_group visit site;
  model change_log_concentration = delivery_log_concentration site group*visit  / ddfm=sat;
  repeated visit / subject=subject type=UN;
  lsmeans group*visit / diffs cl obsmargins;
run;
```

Here *change_log_concentration* is the change in log(IgG concentration) from delivery, *delivery_log_concentration* is the log(IgG concentration) at delivery, and *visit* is the study Visit (i.e., 6, 7, and 8).

Least square mean estimates of the change in log(IgG concentration) from delivery with 95% confidence intervals (CI) will be presented at each time-point for each group.

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

4.10 Analysis of Exploratory Safety endpoints (Exploratory endpoints)

Incidence of preterm births will be tabulated descriptive by group.

4.11 Analysis of Immunogenicity (Exploratory endpoints)

The exploratory immunogenicity analysis for this study will be the responsibility of the researchers in MinervaX AB, Sweden.

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5 Multiplicity

Due to the large number of performed tests, the statistical analyses are considered of descriptive and 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 testing results will be considered.

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6 Interim analyses

An interim analysis (safety) will be performed on data collected up to Day 56 from the first 20 participants recruited in South Africa. The interim analysis will focus on safety and tolerability of the GBS-NN/NN2 vaccine in the mother. The following safety endpoints in the mother will be evaluated during the interim safety analysis: local and systemic reactogenicity (headache, sore throat, “flu-like” symptoms, muscle aches, fever in the 72 hours post dose); adverse events; laboratory tests; dipstick urinalysis; vital signs; physical examination. Assessments of the in-utero growth of the babies will also be included.
The interim analyses will be performed without any unblinding for the sponsor and the statistician. An independent designee will be mandated by OnQ research and MinervaX to perform the analysis. The results will be sent directly to the DSMB and TSC members. The DSMB and TSC will send recommendations to the sponsor.

See separate statistical analysis plan for the interim analysis.

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7 Deviations from protocol

- Naming of "ITT" population is changed to "SAF" - definition is unchanged.
- The protocol mentions chi-squared tests for the safety analysis. As no predefined AEs were specified it was decided to keep the analysis of the safety data descriptive.
- Adverse events in the infant was added to the primary safety endpoint.
- To ensure all secondary objectives mentioned in the protocol can be described, the secondary endpoints were extended to include:
    - Geometric mean antibody concentration in maternal blood 6 months post-delivery
    - Geometric mean antibody concentration in infant blood 1, 2, and 3 months post-delivery
- Antibodies to the two fusion Proteins GBS-NN and GBS-NN2 are not measured hence not analysed.
- Incidence of preterm births added as an exploratory safety endpoint.

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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.

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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 version 9.4 or later.

The sponsor's name (MinervaX), protocol number (MVX0005), 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).

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10 Tables, listings, and figures

See below appendix A for table shells of some example tables, with site split as an example.

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11 Change log

Version	Effective date	Reason for revision
FINAL v1.0	02-June-2023	FINAL

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12 References

[1]: “Clinical Study Protocol MVX0005_ZA V3.0 Final dated 20210129”

[2]: “MVX-0005_UG Protocol V2.0-16 Nov 2021_Final_signed”

[3]: https://agesandstages.com/

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13 Appendix A –table shells (example)

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Table xx.x.x Baseline characteristics - Demography (SAF)

		RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx)	Wits (South Africa) (N=xx)	MU-JHU Care Limited (Uganda) (N=xx)	Total (N=xxx)
Gender, n(%)	n	xx	xx	xx	xxx
	Male	x	x	x	x
	Female	xx (xxx.x)	xx (xxx.x)	xx (xxx.x)	xxx (xxx.x)
	Missing	x	x	x	x
Age at screening (years)	n	xx	xx	xx	xxx
	Missing	x	x	x	x
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
Race, n(%)	n	xx	xx	xx	xxx
	Missing	x	x	x	x
	Asian	x	x	x	x
	Black	xx (xx.x)	xx (xxx.x)	xx (xxx.x)	xxx (xx.x)
	Mixed Race	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	White	x	x	x	x
	Other	x	x	x	x
Ethnicity, n(%)	n	xx	xx	xx	xxx
	Missing	x	x	x	x
	Hispanic or Latino	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Not Hispanic or Latino	xx (xxx.x)	xx (xxx.x)	xx (xx.x)	xxx (xx.x)
	Not reported	x	x	x	x

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	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx)	Wits (South Africa) (N=xx)	MU-JHU Care Limited (Uganda) (N=xx)	Total (N=xxx)
Unknown	x	x	x	x

Trial ID: MVX0005, Program name: programs/tbl demo.sas, Run date: ddmmyyyy, Data Transfer: ddmmyyyy

N = Number of participants in analysis population.
% = Percent of participant population
SD = standard deviation, CI= confidence interval
Min= minimum, Max= maximum

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Table xx.x.x Overall summary of adverse events details: (SAF)

	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n(%)	E	Wits (South Africa) (N=xx) n(%)	E	MU-JHU Care Limited (Uganda) (N=xx) n(%)	E	Total (N=xxx) n(%)	E
All events	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxxx
Ongoing AE ?								
Yes	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
No	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxxx
Severity								
Mild	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xx.x)	xxx	xxx (xx.x)	xxx
Moderate	xx (xx.x)	xx	x (xx.x)	xx	xx (xx.x)	xxx	xxx (xx.x)	xxx
Severe	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Action taken								
Concomitant Med Added Or Changed	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxx
No Action Taken	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Other	xx (xx.x)	xx	xx (xx.x)	xx	x (xx.x)	x	xx (xx.x)	xx
Procedure Required	xx (xx.x)	xx	x (xx.x)	x	xx (xx.x)	xx	xx (xx.x)	xx
Study Mediation Permanently Stopped	x (x.x)	x	x (x.x)	x	x (x.x)	x	x (x.x)	x
Other action taken								
Xxx	x (x.x)	x	X (x.x)	x	X (x.x)	x	x (x.x)	x
Relation to study medication								
Not Related	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxxx
Related	x (x.x)	x	x (x.x)	x	x (xx.x)	xx	xx (x.x)	xx
Outcome								
Fatal	x (x.x)	x	x (x.x)	x	x (x.x)	x	x (x.x)	x
Not Recovered / Not Resolved	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx

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	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n(%)	E	Wits (South Africa) (N=xx) n(%)	E	MU-JHU Care Limited (Uganda) (N=xx) n(%)	E	Total (N=xxx) n(%)	E
Recovered / Resolved	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxxx
Recovered / Resolved With Sequelae	x (x.x)	x	x (x.x)	x	x (x.x)	x	xx (x.x)	xx
Recovering / Resolving	x (x.x)	x	x (x.x)	x	x (x.x)	x	x (x.x)	x
Serious AE ?								
Yes	xx (xx.x)	xxx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
No	xx (xx.x)	xxx	xx (xx.x)	xxx	xx (xxx.x)	xxx	xxx (xx.x)	xxx
Fatal ?								
Yes	x (x.x)	x	x (x.x)	x	x (x.x)	x	x (x.x)	x
No	xx (xx.x)	xxx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Immediately life threatening								
Yes	x (x.x)	xx	x		x (x.x)	x	x (x.x)	xx
No	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Requiring hospitalisation or prolonged hospitalisation								
Yes	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
No	x (xx.x)	xx	x (x.x)	x	xx (xx.x)	xx	xx (xx.x)	xx
Persistent or significant disability/incapacity?								
No	xx (xx.x)	xxx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Congenital anomaly/birth defect								
Yes	x (x.x)	x	x (x.x)	x	x (x.x)	x	x (x.x)	x
No	xx (xx.x)	xxx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx
Other medically important serious event ?								
Yes	x (x.x)	x	x (x.x)	x	xx (xx.x)	xx	xx (x.x)	xx
No	xx (xx.x)	xxx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xxx

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	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n(%)	E	Wits (South Africa) (N=xx) n(%)	E	MU-JHU Care Limited (Uganda) (N=xx) n(%)	E	Total (N=xxx) n(%)	E

Trial ID: MVXxxxx, Program name: programs/t xx x x.sas, Run date: ddmmyyyy, Data Transfer : ddmmyyyy

E: number of adverse events, N: Number of participants in analysis population,
n: Number of participants with one or more adverse events
%: Percentage of participants with one or more adverse events.

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Table xx.x.x Baseline Descriptive statistics – Vital Signs (SAF).

		RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx)	Wits (South Africa) (N=xx)	MU-JHU Care Limited (Uganda) (N=xx)	Total (N=xxx)
Heart rate (bpm)	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
	Missing	x	x	x	x
SBP (mmHg)	n	xx	xx	xx	xxx
	Mean (SD)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (xx.x)	xxx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x
	xx % CI lower ; upper	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x

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	Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
	Missing	x	x	x	x
DBP (mmHg)	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing	x	x	x	x
Axillary temperature (celsius)	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing	x	x	x	x

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Maternal Height (cm)	n	xx	xx	xx	xxx
	Mean (SD)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x
	xx % CI lower ; upper	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x
	Min ; Max	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x
	Missing	x	x	x	x
Maternal weight(kg)	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xx.x	xx.x ; xxx.x
	Missing	x	x	x	x
Maternal BMI (kg/m2)	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x

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	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing	x	x	x	x
Mid Upper Arm Circumference	n	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing	x	x	x	x
Foetal heart rate(bpm)	n	xx	xx	xx	xxx
	Mean (SD)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (x.x)	xxx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x
	xx % CI lower ; upper	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x
	Min ; Max	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x	xxx.x ; xxx.x

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	Missing	x	x	x	x
Foetal movement in last xx hrs	n	xx	xx	xx	xxx
	Yes	xx (xxx.x)	xx (xx.x)	xx (xxx.x)	xxx (xx.x)
	No	x (x.x)	x (x.x)	x (x.x)	x (x.x)
	Missing	x	x	x	x
Symphysis Fundi height(cm)	N	xx	xx	xx	xxx
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Standard error of the mean	x.x	x.x	x.x	x.x
	Median	xx.x	xx.x	xx.x	xx.x
	xx % CI lower ; upper	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Min ; Max	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x	xx.x ; xx.x
	Missing	x	x	x	x

Trial ID: MVX0005, Program name: programs/tbl_vs_site.sas, Run date: ddmmmyyy , Data Transfer : ddmmmyyyy

N = Number of participants in analysis population.
n: Number of participants fulfilling criteria, % = Percent of participants

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Table xx.x.x Adverse Events frequencies (numbers of participants with AE), overall and per site - Mothers (SAF).

System Organ Class Preferred Term	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n (%) E	Wits (South Africa) (N=xx) n (%) E	MU-JHU Care Limited (Uganda) (N=xx) n (%) E	Total (N=xxx) n (%) E
Any Adverse Events	xx (xx.x) xxx	xx (xx.x) xxx	xx (xx.x) xxx	xxx (xx.x) xxx
All SOC	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xxx	xxx (xx.x) xxx
All preferred Terms	xx (xx.x) xx	x (x.x) x	xx (xx.x) xx	xx (xx.x) xx

Trial ID: MVX0005, Program name: programs/tbl ae n.sas, Run date: ddmmyyyy , Data Transfer : ddmmyyyy

N = Number of participants in analysis population.
n = Number of participants with an Adverse Event. E = Number of Events.
In case no MedDRA information is available, System Organ Class will indicate this by 'Not coded' and
Preferred Term will present the reported term instead.

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Table xx.x.x Adverse Events frequencies (numbers of participants with AE), overall and per site - Babies (BSA).

System Organ Class Preferred Term	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n (%) E	Wits (South Africa) (N=xx) n (%) E	MU-JHU Care Limited (Uganda) (N=xx) n (%) E	Total (N=xxx) n (%) E
Any Adverse Events	xx (xx.x) xxx	xx (xx.x) xxx	xx (xx.x) xxx	xxx (xx.x) xxx
All SOC	xx (xx.x) xxx	xx (xx.x) xx	xx (xx.x) xx	xxx (xx.x) xxx
All preferred terms	xx (xx.x) xxx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xxx

Trial ID: MVX0005, Program name: programs/tbl ae n.sas, Run date: ddmmyyyy , Data Transfer : ddmmyyyy

N = Number of participants in analysis population.
n = Number of participants with an Adverse Event. E = Number of Events.
In case no MedDRA information is available, System Organ Class will indicate this by 'Not coded' and Preferred Term will present the reported term instead.

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Table xx.x.x Serious Adverse Events frequencies (numbers of participants with SAE), overall and per site - Mothers (SAF).

System Organ Class Preferred Term	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n (%) E	Wits (South Africa) (N=xx) n (%) E	MU-JHU Care Limited (Uganda) (N=xx) n (%) E	Total (N=xxx) n (%) E
Any Serious Adverse Events	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xxx
All SOC	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
All preferred terms	xx (xx.x) xx	x (xx.x) x	x (x.x) x	xx (xx.x) xx

Trial ID: MVX0005, Program name: programs/tbl ae n.sas, Run date: ddmmyyyy , Data Transfer : ddmmyyyy

N = Number of participants in analysis population.
n = Number of participants with an Adverse Event. E = Number of Events.
In case no MedDRA information is available, System Organ Class will indicate this by 'Not coded' and
Preferred Term will present the reported term instead.

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Table xx.x.x Serious Adverse Events frequencies (numbers of participants with SAE), overall and per site - Babies (BSA).

System Organ Class Preferred Term	RMPRU/Wits VIDA Research Unit Clinic (South Africa) (N=xx) n (%) E	Wits (South Africa) (N=xx) n (%) E	MU-JHU Care Limited (Uganda) (N=xx) n (%) E	Total (N=xxx) n (%) E
Any Serious Adverse Events	xx (xx.x) xx	x (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
All SOC	xx (xx.x) xx	x (x.x) x	xx (xx.x) xx	xx (xx.x) xx
All preferred term	x (x.x) x	x	x (xx.x) x	xx (x.x) xx

Trial ID: MVX0005, Program name: programs/tbl ae n.sas, Run date: ddmmyyyy , Data Transfer : ddmmyyyy

N = Number of participants in analysis population.
n = Number of participants with an Adverse Event. E = Number of Events.
In case no MedDRA information is available, System Organ Class will indicate this by 'Not coded' and
Preferred Term will present the reported term instead.