Clinical study protocol

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

Coordinating principal investigator: [redacted]

Sponsor protocol number: **MVX0004**

EudraCT number: **2021-003214-40**

Investigational product name: **GBS-NN/NN2**

Development phase: **Phase II**

Sponsor's Chief medical officer: [redacted]

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The study will be conducted according to the protocol and in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

Signature of sponsor

This study protocol was subjected to critical review. The information it contains is consistent with the current knowledge of the benefits and risks of the investigational medicinal product, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

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Signature of study coordinating and site principal investigator

This study protocol was subjected to critical review and has been approved by the sponsor. The information it contains is consistent with the current knowledge of the benefits and risks of the investigational medicinal product, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

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List of abbreviations and definition of terms

AE	Adverse event
AESI	Adverse event of special interest
Alp	Alpha like protein family; Rib, Alp1, AlpC, Alp2, Alp3 and Alp4.
BIG	Baby immunogenicity set
BMI	Body mass index
BPP	Baby per protocol set
BSA	Baby safety analysis set
CI	Confidence interval
CMO	Corporate medical officer
CM	Concomitant medication
CRF	Case report form
CRO	Clinical research organisation
CS	Clinically significant
CSR	Clinical study report
CTA	Clinical trial application
DK	Denmark
DP	Drug product
DSUR	Development safety update report
eCRF	Electronic case report form
eDiary	Electronic diary
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOD	Early-onset disease
EudraCT	(European Union Drug Regulating Authorities Clinical Trials) European Clinical Trials Database
FAS	Full analysis set
FSFV	First subject's first visit
GA	Gestational age
GBS	Group B Streptococcus
GCP	Good Clinical Practice
GLP	Good laboratory practice
GMC	Geometric mean concentration
GMCR	Geometric mean concentration ratio
GMP	Good manufacturing practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IAP	Intrapartum antibiotic prophylaxis
IB	Investigator's brochure
ICH	International Council for Harmonisation

ICH GCP E6 (R2)	ICH GCP (E6) Revision 2, last updated 15-Dec-2016.
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intention-to-treat
LOD	Late-onset disease
LSLV	Last subject's last visit
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]
PD	Pharmacodynamic(s)
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
PROM	Prelabour rupture of membranes
PV	Pharmacovigilance
QP	Qualified person
RGL	Regulatory green light
Rib	Protein expressed on the surface of GBS
RSI	Reference safety information
SA	South Africa
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TMF	Trial master file
UK	United Kingdom
UTI	Urinary tract infection
WHO	World Health Organization

1 Protocol synopsis

Title	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.
Study code	MVX0004
EudraCT No.	2021-003214-40
Study phase	Phase II
Coordinating (study) Principal investigator	[redacted] MD, St George's University of London, UK
Coordinating (study) Principal investigator site	Institute of Infection and Immunity, St George's University of London, UK
Primary objective	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, according to four vaccination regimens during pregnancy, between the GBS-NN/NN2 and placebo groups: • Group 1: 2 doses GBS-NN/NN2 at 26 & 30 weeks GA • Group 2: 2 doses GBS-NN/NN2 at 22 & 26 weeks GA • Group 3: 2 doses GBS-NN/NN2 at 22 & 30 weeks GA • Group 4: 1 dose GBS-NN/NN2 at 26 weeks GA • Group 5: Placebo at 22, 26 & 30 weeks GA
Key secondary objective(s) (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.
Secondary objective(s) (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

Exploratory objective(s)	• [redacted] • [redacted] • [redacted]
Primary endpoint	The following primary endpoint(s) will be evaluated, by group: • Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in cord blood from each baby: o The geometric mean antibody concentrations at birth will be calculated o 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
Key secondary endpoint(s) (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
Secondary endpoint(s) (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: o The geometric mean antibody concentrations at delivery, and geometric mean concentration ratios relative to baseline will be calculated o 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 o 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 • The ratios of antibody concentrations between maternal and cord blood at delivery will be calculated 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: o The geometric mean antibody concentrations at 1 month and 3 months after birth will be calculated o 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

<table>
<tr><td>Exploratory endpoint(s)</td><td>The following exploratory immunogenicity endpoints will be evaluated:
[redacted]</td></tr>
<tr><td>Study design</td><td>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 woman, assessing IgG specific to AlpN proteins in cord blood and maternal blood, and the safety profile in mother and the baby up to 6 months post-delivery.
Each dose of 0.5 mL GBS-NN/NN2 will contain 50 µg of GBS-NN and 50 µg of GBS-NN2 and will be given by intramuscular injection.
Group 1 will be 60 pregnant women who will receive one injection of placebo (saline) followed by two injections of the investigational vaccine GBS-NN/NN2.
Group 2 will be 60 pregnant women who will receive two injections of GBS-NN/NN2 followed by one injection of placebo (saline).
Group 3 will be 60 pregnant women who will receive one injection of GBS-NN/NN2 followed by one placebo (saline) and a second injection of GBS-NN/NN2.
Group 4 will be 60 pregnant women who will receive one injection of placebo (saline) followed by one injection of GBS-NN/NN2 and a second injection of placebo (saline).
Group 5 will be 30 pregnant women who will receive three injections of placebo (saline).
<table>
<tr><th></th><th>Group 1</th><th>Group 2</th><th>Group 3</th><th>Group 4</th><th>Group 5</th></tr>
<tr><td>No. Subjects</td><td>60</td><td>60</td><td>60</td><td>60</td><td>30</td></tr>
<tr><td>GA 22 weeks</td><td>PLACEBO (saline)</td><td>GBS-NN/NN2</td><td>GBS-NN/NN2</td><td>PLACEBO (saline)</td><td>PLACEBO (saline)</td></tr>
<tr><td>GA 26 weeks</td><td>GBS-NN/NN2</td><td>GBS-NN/NN2</td><td>PLACEBO (saline)</td><td>GBS-NN/NN2</td><td>PLACEBO (saline)</td></tr>
<tr><td>GA 30 weeks</td><td>GBS-NN/NN2</td><td>PLACEBO (saline)</td><td>GBS-NN/NN2</td><td>PLACEBO (saline)</td><td>PLACEBO (saline)</td></tr>
</table>
</td></tr>
<tr><td>Study population and planned number of study subjects</td><td>A total of 270 pregnant women are planned to be randomised.</td></tr>
<tr><td>Inclusion criteria:</td><td>1. Healthy pregnant woman above the legally defined age of consent at the time of screening
2. Carrying a normal singleton pregnancy, and is at 21+0 to 23+6 weeks GA at the planned time of the 1st vaccination, as established by first/second trimester ultrasound examination.
3. Properly informed about the study and has given written informed consent and parental consent (for her baby) in accordance with ICH GCP and local legislation prior to the first study intervention
4. Grants access to her own and her baby's study related medical records</td></tr>
</table>

Exclusion criteria:	1. Previous vaccination with an investigational Group B Streptococcus (GBS) Vaccine 2. BMI of <17 or >40 at the time of screening 3. HIV, HBV and/or HCV positive or positive for syphilis 4. Knowingly carrying, at screening, a malformed or genetically abnormal foetus, incl. renal pelvis dilation, single umbilical artery (screening will be undertaken after the ultrasound conducted for the detection of anomalies) 5. Chronic or pregnancy induced hypertension at screening, >1+ protein in urine regardless of blood pressure or 1+ protein in urine and hypertension 6. Experienced a previous stillbirth prior to going into labour 7. Gestational, type 1 or type 2 diabetes 8. Potential placenta previa as per malformation ultrasound scan 9. Rhesus negative and has anti-D antibodies or other potential harmful antibodies 10. Known or suspected allergies to any components of the vaccine including to aluminium or aminoglycoside antibiotics, or an allergic reaction related to a previous vaccination 11. Fever (temperature >37.9°C) on the day of receiving the first dose or an acute infection in the 7 days before the first dose (the first dose can be delayed if gestational age permits) 12. Received systemic steroids in the 6 weeks before the first dose (inhaled and topical steroids are acceptable) 13. Any lesion (including tattoos) at the planned injection site that will impair the assessment of the injection site 14. Received immunosuppressive medication, chemotherapy or radiotherapy in the 24 weeks before the first dose 15. Received blood, blood products, plasma derivatives or any immunoglobulin preparations in the 12 weeks before the first dose 16. Anaemia, haemoglobin (<10 g/dL, 100 g/L, 6.2 mmol/L) 17. Currently breast feeding 18. Received any investigational medicinal product or vaccine in the 12 weeks or 5 half-lives before the first dose 19. Received an approved vaccine within the 4 weeks before the first dose or expects to receive an approved vaccine during the study. Routine vaccinations recommended during pregnancy (e.g., pertussis and influenza) are permitted but every effort should be made to separate routine vaccinations from the trial vaccinations by at least 7 days. 20. Known or suspected immunodeficiency or cancer (leukaemia, lymphoma), or a family history of congenital or hereditary immunodeficiency 21. History or presence of uncontrolled cardiovascular disease, pulmonary, hepatic, gall bladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, or autoimmune disease 22. History of, or current drug or alcohol abuse 23. In the opinion of the investigator not suitable for inclusion in the study 24. The pregnancy is considered high risk by treating physicians

Investigational medicinal products	Group B Streptococcus Vaccine (GBS-NN/NN2) mixed with Alhydrogel. The final unit dose of GBS-NN/NN2 will contain a sterile suspension of injection of 50 µg of the two fusion proteins in an isotonic buffer and 0.5 mg of aluminium in a volume of 0.5 mL. The Placebo will be 0.9 % saline sterile solution for injection, purchased locally by the investigational sites. The Vaccine and Placebo are visibly distinguishable; therefore, to ensure the blinding of the study is maintained, it will be ensured that a separate unblinded study team will administer the injections, or that syringes with opaque tape will be used, preventing the contents being identified.
Dosages and route of administration	Each injected dose of 0.5 mL GBS-NN/NN2 contains 50 µg of GBS-NN, 50 µg of GBS-NN2 and 0.5 mg of aluminium for all groups and vaccination regimens. Each injected dose of 0.5 mL Placebo consists of 0.9 % saline for all groups and vaccination regimens. Administration will be by intramuscular injection, preferably into the non-dominant arm. The dominant arm may be used if it is not possible to administer into the non-dominant arm e.g., due to an ongoing injection site reaction, or a tattoo making assessment of the injection site difficult.
Statistical methods	For the assessment of adequate sample size, data from earlier phase studies including healthy females of childbearing potential exposed to double vaccination was utilized. Observed seroprotection levels, as defined by a cut-point of 1.0 µg/mL, was above 95% across the 4 relevant antigens. With a group size of 60, the power of a non-inferiority test with Group 1 as reference and using a 15% point limit would then be above 90% for all 4 antigens, assuming equal responses in Groups 1, 2 and 3. The primary objective of the study will be assessed using the following endpoints, based on cord blood in the eligible set of newborn children: • IgG antibody concentrations specific to each of the four chosen AlpN proteins • Seroprotection rates as defined by AlpN-specific IgG concentrations being above the following cut points: 0.1, 0.2, 0.5, 1, 2, 4 and 8 µg/mL The comparison will be conducted as a series of non-inferiority tests, for each choice of antigen, endpoint and cut-point with two pre-defined margins: • Seroprotection: 15% points (0.15) on the absolute scale • IgG concentrations: a GMC ratio of 2/3 is considered adequate Group 1 (1st dose 26 weeks GA; 4 weeks interval) will be considered as the reference group. Due to the large number of performed tests, these non-inferiority procedures are considered of non-confirmatory nature and thus no control for multiplicity is applied. The main purpose of testing is to guide selection of the vaccination schedule to carry forward. In a combined analysis across Groups 1 to 4, maternal IgG concentrations pre-dose (i.e. 4 weeks after each vaccination) and at delivery, will be analysed using a log-normal model with repeated measurements within subject, vaccination group and visit as factors, possibly allowing for changing variance across visits and visit times group interactions. Using this model, the ratio of geometric mean concentrations in the vaccination groups can be derived. Other endpoints, in particular safety, will be summarized using descriptive statistics. An early analysis of study data will be performed based on primary and key secondary endpoints available up to 72 hours after delivery (Visit 8).

2 Introduction

2.1 Background Group B streptococcus (GBS) infection and disease

Streptococcus agalactiae, also referred to as Lancefield's group B Streptococcus (GBS), is a Gram-positive diplococcus that colonizes the gastrointestinal and genital tracts of up to 30% of women. Normally, a commensal it does not cause clinical problems for colonized women. However, in pregnant women who are colonized with GBS there is a significantly higher occurrence of postpartum fever and endometritis compared to women who are not colonised. GBS is the most common causes of life-threatening invasive bacterial infections in neonates and young infants. Infections can result in neonatal sepsis, pneumonia and meningitis, in infants living in diverse regions (Fluegge et al. 2006; Lin et al. 2018; Neto 2008; Rivera et al. 2015), and is associated with significant mortality and morbidity, including long-term neuro-developmental sequelae (Kobayashi et al. 2016). GBS is also associated with disease in adults particularly in the elderly and adults who are immunosuppressed. GBS is also a cause of mastitis and perinatal puerperal infections (Kobayashi et al. 2016; Nuccitelli, Rinaudo, and Maione 2015; Kvist et al. 2008; Pass, Gray, and Dillon 1982; Shet and Ferrieri 2004).

GBS infection in new-borns is usually classified as early-onset disease (EOD), occurring during the first 6 days of life and late-onset disease (LOD) occurring between day 7 to 89 days of life. It is estimated that 60–90% of EOD occurs on the first day of life following in-utero infection (Verani, McGee, and Schrag 2010). Ascending infection of the vagina leads to infection of the chorioamniotic membrane and infection of the amniotic fluid and subsequent transmission to the foetus via the bronchopulmonary tree leading to EOD manifest as respiratory distress and septicaemia. Late onset disease may be caused by nosocomial, horizontal transmission from mother to baby or by transmission through breast milk. In late-onset GBS disease, the GBS bacteria adhere to infant mucosal surfaces, gaining access to the blood stream and crossing the blood brain barrier, leading to meningitis, which is a more common presentation of LOD.

The global incidence per 1 000 live births of invasive GBS disease in infants <90 days of age was recently estimated to be 0.49 (Madrid et al. 2017), which is slightly lower than the previous estimate of 0.53 (95% confidence interval (CI) 0.44 – 0.62) with a case fatality ratio of 9.6% (Edmond et al. 2012).

In the USA, the incidence of EOD has declined significantly (>80%) since the early 1990s through effective execution of secondary preventative strategies, i.e., screening all women at 35 to 37 weeks gestation and administering intrapartum antibiotic prophylaxis (IAP) to women determined to be colonised. IAP require intravenous antibiotics administered for at least 4 hours before delivery.

Worldwide in 2015, it was estimated that there were 205,000 infants with early-onset disease and 114,000 with late-onset disease, leading to 90,000 deaths in infants. There were 33,000 cases of invasive GBS disease in pregnant or postpartum women, and 57,000 foetal infections/stillbirths (Seale, Bianchi-Jassir, et al. 2017).

It has been estimated that there are some 2.6 million stillbirths world-wide annually, and that GBS accounts for 1% of stillbirths in developed countries but as much as 4% in sub-Saharan African

countries. In Africa there are 1.1 million stillbirths a year; hence GBS could be responsible for 44,000 stillbirths (Seale, Blencowe, et al. 2017). In addition, maternal GBS colonization has been associated with preterm delivery (Bianchi-Jassir et al. 2017), but there are multiple confounding factors, and the incidence has not been determined.

In addition to the inability of IAP to completely eradicate EOD and prevent GBS-induced LOD, stillbirth and preterm labour, the widespread use of antibiotic prophylaxis in GBS prevention has been associated with the emergence of antibiotic resistance in GBS, and an increase in the number of neonatal infections with antibiotic resistant strains of other bacteria such as *E. coli*. Penicillin remains the preferred antibiotic prophylaxis, but clinical isolates with reduced sensitivity to penicillin due to mutations in penicillin-binding proteins have emerged over recent years (Kimura et al. 2008). An alarming finding is that the emerging patterns of mutations are identical to those observed for *S. pneumoniae* prior to the breakthrough of widespread true penicillin resistance for that pathogen (Dahesh et al. 2008; Nagano et al. 2009). Full breakthrough of penicillin resistance in GBS will lead to a dramatic increase in the incidences of EOD, potentially returning the world to pre-IAP levels, as well as creating a serious problem when having to treat such resistant infections. In addition, wide-spread resistance to antibiotics other than penicillin already exists in GBS isolates (CDC, 2010).

Prevention of GBS infections in new-born babies and finding a safe and efficacious alternative to current antibiotic prophylactic strategies, therefore, represent a large unmet medical need.

2.2 Rationale for GBS vaccination during pregnancy

A vaccine against GBS, for use in pregnant women, enabling passive transfer of high concentrations of neutralizing anti-GBS antibodies to the foetus, and persisting for the first 3-6 months after birth, when the babies are most at risk, seems the obvious choice to address such unmet medical need. An effective vaccine will significantly reduce the need for current antibiotic prophylaxis during childbirth and hence, reduce the risks associated with emerging antibiotic resistance. In addition to having an effect on EOD, a vaccine will also potentially have an effect on *in-utero* infections (depending on the timing of the vaccination), reducing the incidence of stillbirths and preterm deliveries caused by GBS, as well as reducing the incidence of LOD infections by inducing persistent circulating IgG antibodies in the infant; none of these adverse outcomes of pregnancy are prevented through current IAP therapy.

From the literature, there is an association between GBS urinary tract infections (UTIs) during pregnancy, and premature rupture of membranes (PROM), preterm delivery and chorioamnionitis (Thomsen, Mørup, and Hansen 1987; Anderson et al. 2007). The incidence of GBS UTI during pregnancy is in the range of 1 to 2% of all pregnancies, and some 20-40% of these pregnancies result in preterm deliveries (Thomsen, Mørup, and Hansen 1987), which negatively affect pregnancy outcomes and carry extensive healthcare and social costs. A vaccine administered in the second trimester, capable of preventing GBS induced PROM and preterm delivery, would prevent some 45,000 such cases annually in Europe and the US. The global burden of GBS infection leading to premature delivery has been estimated at up to 3.5 million cases per year (Seale, Bianchi-Jassir, et al. 2017).

In addition, mothers provide antibodies (IgG and IgA) to their newborn babies in breast milk. A vaccine that can induce secretory IgA active against GBS as well as IgG, may potentially provide longer duration of protection against infection through the transfer of antibodies, particularly IgA, in breast milk.

2.3 Rationale for the GBS-NN/NN2 vaccine

GBS is an encapsulated Gram-positive bacterium, divided into ten different serotypes (Ia, Ib, II-IX) classified based on their capsular polysaccharides. Serotypes Ia and III are the clinically most important, and serotypes Ia, Ib, II, III, IV and V together cover approximately 95% of all colonizing isolates recovered from pregnant women. Vaccine development has focused on inducing immune responses against these capsular polysaccharides, drawing parallels from the development of pneumococcal vaccines.

In addition to the immunogenic capsular polysaccharide coat, GBS expresses a family of six, immunogenic surface proteins, termed the Alpha like proteins (Alp) proteins. The family consist of Rib, Alp1, AlpC, Alp2, Alp3 and Alp4. These surface proteins are anchored in the membrane through the C-terminus, have a region of multiple repeated domains extending out through the polysaccharide capsule, ending in a functionally active N-terminal domain. The N-terminal domains bind to $\alpha 1\beta 1$ integrin and glycosamino glycans facilitating the invasion of epithelial cells and the crossing of the blood-brain barrier. MinervaX has developed a vaccine utilising the N-terminals of four of the six Alpha like proteins. The four AlpN proteins are combined into two fusion proteins GBS-NN, which contains the Rib and AlpC N-terminal domains, and GBS-NN2 which contains the Alp1 and Alp2 N-terminal domains. These four terminal proteins cover over 95% of the strains found to be pathogenic in humans. The Alp3 protein has an identical N-terminal domain to Alp2, hence both Alp2N and Alp3N are covered by the Alp2/3N protein. Alp4 has not been found in any clinical isolates to date, and therefore, has not been included. Antibodies directed against the N-terminal domains are protective against GBS infections in *in vitro* experiments and *in vivo* animal models. The Rib and AlpC proteins are the most prevalent members of the Alp-protein family in the pathogenic strains and antibodies against the N-terminal domains of these proteins also cross react with Alp1-3 N-terminal domains to some extent.

The four proteins, Rib, Alp1, AlpC and Alp2/3, are found on most isolates of all serotypes (Ia, Ib, II, III, IV, V, VI, VII, VIII and IX). Antibodies directed against the vaccine were found to recognize nearly 100% of 154 clinical isolates of serotypes Ia, Ib, II, III and V tested for antibody binding. Furthermore, the Rib protein is expressed on most serotype III strains, which cause almost all cases of meningitis, and by all strains of a hyper-virulent type III clone (Baker and Edwards 2003; Brimil et al. 2006; Brochet et al. 2006).

Naturally occurring antibodies against the full-length Rib, Alp1, AlpC and Alp2/3 proteins are found in pregnant and non-pregnant women, probably due to exposure to GBS from colonization or infections such as GBS urinary tract infections, and such antibodies are efficiently transferred to their babies *in-utero*.

Importantly, a correlation between high concentrations of such antibodies directed against the N-terminal domains, in the mothers and their new-borns are associated with a reduced incidence of invasive GBS disease in the new-borns (Larsson, Stålhammar-Carlemalm, and Lindahl 1999).

A case-control study in neonates with invasive GBS disease and relevant controls of neonates born to mothers carrying the same GBS isolates, but not contracting GBS disease, has shown that a preliminary estimate for the predicted threshold for 90% protection against invasive disease is a concentration of IgG specific to the N-terminal domain of the Rib protein of 0.52 µg/ml, and for Alp1 specific IgG: 0.12 µg/ml (Minervax Internal Report MVX012).

For details on the physical, chemical and pharmaceutical properties of the GBS-NN/NN2 vaccine, please refer to the IB.

2.4 Summary of non-clinical and clinical studies

Administering a vaccine containing RibN and AlpCN proteins elicit protective immunity in animal models when administered with alum, an adjuvant accepted for human use (Larsson, Stålhammar-Carlemalm, and Lindahl 1999; Stalhammar-Carlemalm et al. 2007), and in consequence, these proteins are of interest for vaccine development.

The N-terminal regions of the Rib and AlpC have been found to elicit a very potent and protective immune response against GBS in mice, which is even more potent than the immune response induced by the repeat regions of the Rib and AlpC proteins (Gravekamp et al. 1996; Gravekamp et al. 1997; Stalhammar-Carlemalm et al. 2007). Furthermore, the GBS-NN fusion protein induce opsonic antibodies against prototype strains, independent of the serotypes, protect adult mice against lethal challenges with prototype strains of serotypes Ia, Ib, II, and III, following direct vaccination, and, most importantly, protect new-born pups born to female mice, vaccinated with GBS-NN, when the pups are challenged with lethal doses of prototype strains of serotypes Ia and III, 12-48 hours after birth (Stalhammar-Carlemalm et al. 2007).

MinervaX generated an initial GBS vaccine candidate, GBS-NN, based on the N-terminal domains of Rib and AlpC surface proteins of GBS, which was administered to 183 healthy non-pregnant women, in a two-part, 240 participant, placebo-controlled phase I study (MVX13211) conducted in the UK.

The clinical study showed the vaccine to be well tolerated with a good safety profile and to be immunogenic, (generating IgG and IgA antibodies) when 2 doses of 50 µg or one or two doses of 100 µg were administered with the adjuvant Alhydrogel®. For the 2 dose regimens, the interval between doses was 4 weeks. Geometric mean antibody concentrations, 8 weeks after the second vaccination of IgG against GBS-NN were: 2 doses of 50 µg 16.9 µg/mL; 2 doses of 100 µg 15.5 µg/mL; 1 dose of 100 µg 3.0 µg/mL, supporting the conclusions that a two-dose vaccination regimen should continue to be evaluated, and that a dose level of 50 µg is sufficient to provide a maximal response.

Detailed assessments of the functionality of the IgG antibodies generated in the study *in vitro* identified, that the degree of cross reactivity with the other two N-terminal proteins Alp1 and

Alp2/3, was not as robust as anticipated, and therefore it was concluded that for a GBS protein vaccine to be effective, four N-terminal protein domains need to be included.

Hence, MinervaX modified the vaccine candidate to contain the four N-terminal proteins: RibN, AlpCN, Alp1N and Alp2/3N. This vaccine has been designated GBS-NN/NN2. The GBS-NN/NN2 vaccine candidate consists of two recombinant fusion proteins containing the two N-terminal regions of the Rib and AlpC proteins (GBS-NN) and the two N-terminal regions of the Alp1 and Alp2/3 proteins (GBS-NN2). As Alp2 and Alp3 have identical N-terminals, Alp 2/3N is also referred to as Alp2N.

In a placebo-controlled phase I study (MVX0002) investigating GBS-NN/NN2 in 60 healthy, non-pregnant women in the UK, 48 received the vaccine at two different dose levels (GBS-NN/NN2 with 25 µg or 50 µg of each protein), and 12 received placebo. All participants in the two groups received two vaccinations 4 weeks apart. The vaccine was immunogenic, well tolerated with a good safety profile, inducing high IgG responses at both dose levels with trends indicating a better overall response to the 50 µg dose; hence, it was decided to continue the development of the 50 µg dose. For the 50 µg dose, the geometric mean concentrations of IgG against GBS-NN were 21.3 µg/mL and against GBS-NN2 38.7 µg/mL, 4 weeks after the second dose. 8 weeks after the second dose, the IgG concentrations were 17.1 µg/mL for GBS-NN and 29.9 µg/mL for GBS-NN2, and more than 95% of evaluable subjects had an IgG concentration >1 µg /mL against all four N-terminal proteins: RibN, Alp1N, Alp2N and AlpCN.

[redacted]

In both completed phase I studies, in healthy, non-pregnant women, the primary endpoint was 8 weeks after the second vaccination, estimated to be the approximate time of delivery for a pregnant woman vaccinated in the third trimester, if doses are administered approximately at 26 and 30 weeks of gestational age (GA).

A placebo-controlled phase II study (MVX0005) in up to 200 pregnant women in South Africa and Uganda is currently ongoing. The first dose of 50 µg GBS-NN/NN2 is administered at 26-30 weeks GA, followed by the second dose 4 weeks later. Two groups of 80 pregnant women, either living with HIV or who do not have HIV, are receiving vaccine, while 2 x 20 pregnant women (with or without HIV) are receiving placebo. The co-primary safety objective in this study is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine in the women and their new-born babies, from vaccination up to delivery/birth, whereas comparison of the transfer rates of vaccine specific IgG antibodies, from the mother to the baby at delivery/birth, between the groups of women living with and without HIV is the co-primary immunogenicity objective.

An open, phase II, booster study (MVX0003) investigating the safety and immunogenicity of a single booster dose of 50 µg GBS-NN/NN2 in the UK is currently under development and scheduled to start in the latter half of 2021. This study is a follow-on study to MVX0002. The non-pregnant women, who received either two doses of 25 or 50 µg GBS-NN/NN2 or placebo (with 4 weeks interval) in the initial study, are being invited to return to receive a single booster vaccination

1 to 5 years after the primary vaccination course. The timing of the booster dose allows for, evaluation of the feasibility of administering a single booster vaccination in pregnancies, subsequent to the pregnancy in which the primary course was administered.

For more detailed information on non-clinical and clinical studies, please refer to the IB.

2.5 Rationale for the present clinical study

MVX0004 is a phase II placebo-controlled study. The 50 µg GBS-NN/NN2 vaccine will be administered to healthy pregnant women.

The study will be conducted in compliance with ICH GCP E6 (R2) and applicable regulatory requirements.

The overall purpose of the study is to determine how four investigated vaccination regimens affect the concentrations of IgG antibodies, against the four AlpN proteins, in cord blood, namely, the vaccination regimens of; two doses at 22- and 26-weeks GA, 22- and 30-weeks GA, 26- and 30-weeks GA, and a single dose at 26 weeks GA, all doses administered by intramuscular injection.

Potentially, vaccination from mid-second trimester may have clinical advantages. A time interval of 8 weeks between the two doses might improve the immunological response in the mother, resulting in higher antibody concentrations in the baby when compared to a 4-week dosing interval. To be able to administer 2 doses 8 weeks apart dosing earlier in pregnancy will be necessary. If the antibody concentrations are similar, it would indicate that a flexible dose interval of 4 to 8 weeks between doses would be effective allowing greater flexibility in dosing. Dosing earlier in pregnancy will also have a potential advantage in reducing GBS induced preterm delivery between 30- and 37-weeks GA. The immune response to a vaccination course where the first vaccination is administered at 22- to 24- weeks GA will result in higher concentrations of antibodies at 30-weeks GA than a vaccination course where the first vaccination is administered at 26- to 28-weeks GA, and therefore may provide protection against adverse outcomes of pregnancy. Efficacy is not being explored in the current study, which is designed to assess the immune response at delivery.

The immunogenicity and safety of 50 µg GBS-NN/NN2 administered according to the four vaccination regimens will be evaluated, comparing the concentrations of IgG specific to the four AlpN proteins (RibN, Alp1N, Alp2N and AlpCN) in cord blood at delivery/birth and adverse event profile comparisons between the groups.

Based on the immunogenicity results of the IgG concentrations specific to the AlpN proteins in cord blood at delivery, as well as the safety results, one of the vaccination regimens will be selected for phase III development. To inform decisions on the vaccination regimen selection as well as the design of a long-term follow-up study, an early analysis of study data for the primary and key secondary endpoints available up to 72 hours after delivery (Visit 8) will be performed. Early analysis of these data will allow to advance the clinical development plan for the GBS-NN/NN2 vaccine, which will help to address the unmet medical need for GBS vaccination during pregnancy.

2.6 Summary of current risk benefit balance

In earlier studies, administration of GBS-NN and GBS-NN/NN2 has been associated with mild to moderate, self-limiting pain at the injection site. No systemic risks have been identified. There have been no reports of significant or persistent reactions at the injection site. The incidence of miscarriage, in pregnancies occurring in the 1-year follow-up period for non-pregnant women, vaccinated with GBS-NN, was in line with the incidence seen in the general population and was comparable between the active and placebo groups with no dose relationship.

Efficacy studies have not been undertaken; therefore, no clear benefits of vaccination have been identified. Data show that GBS-NN/NN2 induces an immune response but it is not known if the immune response is protective against invasive GBS disease in neonates. The immune response generated has been shown to induce IgG1 antibodies; it is IgG1 antibodies that are actively transported across the placenta. An analysis of the opsonophagocytic activity of the antibodies generated against GBS-NN and GBS-NN/NN2 has shown that the antibodies have functional activity. Hence, further development is warranted to facilitate the undertaking of efficacy studies.

GBS-NN/NN2 is presently being investigated in pregnant women (who are either living with HIV or who are HIV negative) in the ongoing MVX0005 study in South Africa. In this study the first dose of vaccine is being administered between 26 and 30 weeks of GA.

In the present study, healthy pregnant women will be vaccinated with GBS-NN/NN2 according to four vaccination regimens. The first dose of vaccine is planned to be administered at 22 weeks of GA for two of the investigated vaccination regimens. This is considered acceptable, based on the current risk benefit balance, and on current vaccination practices in pregnant women for pertussis and influenza vaccine.

Influenza vaccines may generally be administered any time during pregnancy, whereas the recommended timing for pertussis vaccination varies between countries. In Denmark, it is recommended to administer pertussis vaccine in the third trimester, from 29 weeks of GA, whereas in the UK, the recommendation is administration from 16 weeks of GA. Pertussis vaccine is recommended between 20 to 32 weeks of GA (although it can be given up to the time of delivery) in South Africa (SA).

Pertussis and influenza vaccinations, may, be administered in the study as concomitant vaccinations, as per general vaccination practices during pregnancy in Denmark, the UK and SA. It is, however, recommended that the time interval between any concomitant vaccination and the investigational vaccine injections is at least 7 days.

All mothers will receive intrapartum antibiotic prophylaxis (IAP) if clinically indicated. Should any babies develop a GBS infection over the course of the study they will be treated by the hospital's standard of care protocol for such infections.

For more detailed information on the benefit risk balance and on the reference safety information (RSI), please refer to the IB.

3 Study objectives and endpoints

3.1 Primary objective

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, according to four vaccination regimens during pregnancy, between the GBS-NN/NN2 and placebo groups:

- Group 1: 2 doses GBS-NN/NN2 at 26 & 30 weeks GA
  (1st dose given 3rd trimester; 4 weeks interval)
- Group 2: 2 doses GBS-NN/NN2 at 22 & 26 weeks GA
  (1st dose given 2nd trimester; 4 weeks interval)
- Group 3: 2 doses GBS-NN/NN2 at 22 & 30 weeks GA
  (1st dose given 2nd trimester; 8 weeks interval)
- Group 4: 1 dose GBS-NN/NN2 at 26 weeks GA
  (one dose given 3rd trimester)
- Group 5: Placebo at 22, 26 and 30 weeks GA
  (1st placebo dose given 2nd trimester, 4 weeks interval)

3.2 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.

3.3 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

3.4 Exploratory objectives

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

3.5 Primary endpoint(s)

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

- 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

The primary immunological endpoint analysis will include the values of these endpoints at the time of delivery, anticipated to be approximately 18 weeks (4 ½ months) from administration of the first dose at 22 weeks GA, or 14 weeks (3½ months) from administration of the first dose at 26 weeks GA.

If cord blood cannot be obtained, venous infant blood may be collected within 72 hours of birth.

3.6 Key secondary endpoint(s)

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

3.7 Secondary endpoints

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

- Concentrations of IgG antibodies specific to the AlpN proteins in µg/mL in maternal blood:
  - The geometric mean 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 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 between maternal and cord blood at delivery will be calculated

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 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

3.8 Exploratory endpoints

The following exploratory immunogenicity endpoints will be evaluated:

4 Study design and investigational plan

4.1 Study administrative structure

The present study is conducted under the responsibility of the Coordinating (study) and site Principal Investigator (PI) [redacted] Institute of Infection and Immunity, St George's University of London, UK

The sponsor of the study is MinervaX ApS, Copenhagen, DK. The clinical project manager and the chief medical officer (CMO) and medical monitor are affiliated with MinervaX.

The clinical monitoring of the study, statistics, data management and pharmacovigilance (SAE reporting) are outsourced to CROs.

The safety and immunogenicity laboratory testing is performed by laboratories at the respective investigational sites in Denmark, the United Kingdom and South Africa or at a central laboratory in the United Kingdom or for the exploratory immunogenicity samples by MinervaX AB in Sweden.

4.2 Overall design

The present study 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.

There will be five treatment groups; three groups of 60 subjects to receive two doses of GBS-NN/NN2 and one of placebo (saline), one group of 60 subjects to receive one dose of GBS-NN/NN2 and two of placebo, and one group of 30 subjects to receive three doses of placebo (saline), please see Table 1.

The study is observer-blind. There will be an unblinded vaccine administering team, separate from the team assessing the participants for safety tolerability and collecting the blood samples for assessment of the immune response. The analysis of the immune responses will be undertaken across all groups, see Section 7.8. For further information on blinding procedures, see Section 5.

An early analysis of study data will be performed based on primary and key secondary endpoints available up to 72 hours after delivery (Visit 8) (see Section 7.12 for details).

Each dose of 0.5 mL GBS-NN/NN2 contains 50 µg of GBS-NN and 50 µg of GBS-NN2 and 0.5 mg of aluminium, for all vaccination regimens and groups, and will be given by intramuscular injection.

Group 1 will be 60 pregnant women who will receive one injection of placebo (saline) followed by two injections of the investigational vaccine GBS-NN/NN2.

Group 2 will be 60 pregnant women who will receive two injections of GBS-NN/NN2 followed by one injection of placebo (saline).

Group 3 will be 60 pregnant women who will receive one injection of GBS-NN/NN2 followed by one placebo (saline) and a second injection of GBS-NN/NN2.

Group 4 will be 60 pregnant women who will receive one injection of placebo (saline) followed by one injection of GBS-NN/NN2 and a second injection of placebo (saline).

Group 5 will be 30 pregnant women who will receive three injections of placebo (saline).

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 weeks	PLACEBO (saline)	GBS-NN/NN2	GBS-NN/NN2	PLACEBO (saline)	PLACEBO (saline)
GA 26 weeks	GBS-NN/NN2	GBS-NN/NN2	PLACEBO (saline)	GBS-NN/NN2	PLACEBO (saline)
GA 30 weeks	GBS-NN/NN2	PLACEBO (saline)	GBS-NN/NN2	PLACEBO (saline)	PLACEBO (saline)

4.3 Study visits and assessments

4.3.1 Schedule of assessments

Table 2 Schedule of assessments for mothers Groups 1, 2, 3, 4 & 5

	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[m]**	**Visit 9[i]**	**Visit 10[i]**	**Visit 11[i]**
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[k]	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		X	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[m]**	**Visit 9[i]**	**Visit 10[i]**	**Visit 11[i]**
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
injection site and immediate AEs[f]												
Instruct 7-day-eDiary		X		X		X						
Review eDiary and transfer data incl. AE/CM			X	X	X	X	X	X				
[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[h]	Visit 10[h]	Visit 11[h]
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 72 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.
h. Visit 9-11 may be performed as home visits.

4.3.2 Description of individual study visits

VISITS FOR MOTHERS:

Screening, Day -14 to Day -1: **Eligibility assessment:**

Obtain informed consent, check eligibility against the in/exclusion criteria, obtain and record demography, medical and obstetric history, current medication (including supplements and over the counter preparations), conduct a full physical examination (respiratory, cardiovascular, gastrointestinal, gross central nervous system, gross musculoskeletal) by a physician, obstetric examination* (fundal height, foetal movement and foetal heart rate), measure and record height and weight (for calculation of BMI), vital signs (heart rate, blood pressure, oral temperature). Collect samples for urinalysis, safety laboratory tests (haematology and serum biochemistry), determination of subject's Hep B, Hep C, HIV and syphilis status (assessment based on results from last samples taken in first trimester, if available, otherwise samples are taken at the screening visit), record result of the last ultrasound for the assessment of the subject's eligibility for inclusion in the study. Subjects will be contacted by phone and informed if they are eligible to proceed from screening, and, if eligible, to confirm the appointment for Visit 1, Day 0, where they will be randomised and assigned to one of the Groups 1 to 5, see Table 1.

Visit 1, Day 0: **Randomisation, 21+0 to 23+6 weeks GA:**

Eligibility check - participants who remain eligible will be randomised according to the randomisation schedule. The randomisation will allocate participants to a specific group. Visit 1, Day 0, is at the planned time of the 1st vaccination which is 21+ 0 to 23+6 weeks GA, as established by first/second trimester ultrasound examination.

Only unblinded study team members, responsible for dispensing and injecting vaccines/placebo, or for checking related procedures and records, will have access to any information regarding the actual products injected to the subjects, and this information will not be revealed to blinded study team members.

The actual injection of vaccine/placebo will be performed by unblinded study team members, or alternatively by blinded study team members by use of syringes with opaque tape, to avoid unblinding during the injections.

The following will be undertaken, and results recorded:

Targeted physical examination* (respiratory, cardiovascular), obstetric examination* (fundal height, foetal movement and foetal heart rate), vital signs (pre- and 30 minutes post-vaccination), urinalysis, pre-vaccination immunogenicity maternal blood sample, and injection of vaccine/placebo. Before the subject leaves the site: Assessment of the injection site, check immediate adverse reactions, and give access to and instruct in the 7-day-eDiary.

Visit 2, Day 3-5:

The following will be undertaken, and results recorded:

Obstetric examination* (foetal movement and foetal heart rate), vital signs, safety laboratory tests, assessment of the injection site and review of the eDiary incl. if measured temperatures within 72 hours lead to permanent discontinuation of vaccination (Section 4.7.2), transfer of AEs and CMs to the eCRF (and instruct to continue eDiary recording). This visit may be planned as a home visit.

Visit 3, Day 26-30:

The following will be undertaken, and results recorded:

Targeted physical examination* (respiratory, cardiovascular), obstetric examination* (fundal height, foetal movement, and foetal heart rate), vital signs (pre- and 30 minutes post-vaccination), urinalysis, safety laboratory tests, assessment of the (previous) injection site, review of the eDiary incl. transfer of AEs and CMs to the eCRF (and instruct for next 7-day-eDiary recording period), check contraindications (Section 4.7.2), assessment of safety laboratory test results from Visit 2, pre-vaccination immunogenicity maternal blood sample, and injection of vaccine/placebo. Before the subject leaves the site: Assessment of the (new) injection site and check immediate adverse reactions.

Visit 4, Day 31-33:

The following will be undertaken, and results recorded:

Obstetric examination* (foetal movement and foetal heart rate), vital signs, safety laboratory tests, assessment of the injection site(s) and review of the eDiary incl. if measured temperatures within 72 hours lead to permanent discontinuation of vaccination (Section 4.7.2), transfer of AEs and CMs to the eCRF (and instruct to continue eDiary recording). This visit may be planned as a home visit.

Visit 5, Day 54-58:

The following will be undertaken, and results recorded:

Targeted physical examination* (respiratory, cardiovascular), obstetric examination* (fundal height, foetal movement and foetal heart rate), vital signs (pre- and 30 minutes post-vaccination), urinalysis, safety laboratory tests, assessment of the (previous) injection sites, review of the eDiary incl. transfer of AEs and CMs to the eCRF (and instruct for next 7-day-eDiary recording period), check contraindications (Section 4.7.2), assessment of safety laboratory test results from Visit 4, pre-vaccination immunogenicity maternal blood sample, and injection of vaccine/placebo. Before the subject leaves the site: Assessment of the (new) injection site and check immediate adverse reactions.

Visit 6, Day 59-61:

The following will be undertaken, and results recorded:

Obstetric examination* (foetal movement and foetal heart rate), vital signs, safety laboratory tests, assessment of the injection sites and review of the eDiary incl. transfer of AEs and CMs to the eCRF (and instruct to continue eDiary recording). This visit may be planned as a home visit.

Visit 7, Day 82-86:

The following will be undertaken, and results recorded:

Obstetric examination* (fundal height, foetal movement and foetal heart rate), height (from screening) and weight (for calculation of BMI), vital signs, safety laboratory tests, immunogenicity maternal blood sample, assessment of the injection sites and review of the eDiary incl. transfer of AEs and CMs to the eCRF (and instruct how to end the eDiary).

Visit 8, Delivery:

The following will be undertaken within 72 hours of delivery, and results recorded:

Vital signs, urinalysis, immunogenicity maternal blood sample, [redacted], and AE and CM check (only medically attended adverse events (MAAEs), adverse events of special interest (AESIs) e.g., GBS disease, autoimmune disease and immune-mediated reactions, or SAEs, and related CMs), according to Table 2.

If a participant delivers, following the first vaccination but before completing all of the pre-delivery follow-up visits, additional blood samples will be collected at delivery for safety laboratory tests.

Visit 9, Day 24-32 Post-delivery:

Targeted physical examination* (respiratory, cardiovascular), height (from screening) and weight (for calculation of BMI), vital signs, urinalysis, [redacted], and AE and CM check (only MAAEs, AESIs or SAEs and related CMs), according to Table 2. This visit may be planned as a home visit.

Visit 10, Day 84-96 Post-delivery:

Vital signs, [redacted] and AE and CM check (only MAAEs, AESIs or SAEs and related CMs), according to Table 2. This visit may be planned as a home visit.

Visit 11, Day 166-194 Post-delivery / End-of-study visit:

Full physical examination (respiratory, cardiovascular, gastrointestinal, gross central nervous system, gross musculoskeletal) by a physician, height (from screening) and weight (for calculation of BMI), vital signs, urine pregnancy test (any participant found pregnant at the end of the study will be followed until delivery, as regards if their baby is healthy at delivery). AE and CM check (only MAAEs, AESIs or SAEs and related CMs), according to Table 2. This visit may be planned as a home visit.

Targeted physical examinations and obstetric examinations of mothers should be performed by appropriately qualified site staff e.g., physician, midwife or nurse.

VISITS FOR BABIES:

Visit 8, Delivery:
The following will be undertaken, and results recorded:

Demography, gestational history (gestational age and gender), physical examination*, head circumference, length, weight, Apgar score (Apgar score at 1, 5 and 10 minutes, available scores will be collected, 'not recorded' will be an option), vital signs (heart rate), immunogenicity cord blood sample (or infant blood sample – heel prick or venous, within 72 hours of birth, if cord blood sample not possible, for target blood volumes for babies see Section 4.4), and AE and CM check.

Visit 9, Day 24-32, Post-delivery:
The following will be undertaken, and results recorded:

Physical examination*, head circumference, length, weight, vital signs, developmental milestones, immunogenicity infant blood sample (heel prick or venous, for target blood volumes for babies see Section 4.4), and AE and CM check. This visit may be planned as a home visit.

Visit 10, Day 84-96, Post-delivery:
The following will be undertaken, and results recorded:

Physical examination*, head circumference, length, weight, vital signs, developmental milestones, immunogenicity infant blood sample (heel prick or venous, for target blood volumes for babies see Section 4.4), and AE and CM check (only MAAEs, AESIs e.g., abnormal development according to developmental milestones, or SAEs, and related CMs), according to Table 3. This visit may be planned as a home visit.

Visit 11, Day 166-194, Post-delivery / End-of-study visit:
The following will be undertaken, and results recorded:

Physical examination*, head circumference, length, weight, vital signs, developmental milestones, and AE and CM check (only MAAEs, AESIs or SAEs, and related CMs), according to Table 3. This visit may be planned as a home visit.

Physical examinations of babies should be performed by appropriately qualified site staff e.g., physician, midwife or nurse.

4.3.3 Safety assessments

The safety of the GBS-NN/NN2 vaccine will be assessed through collection of adverse events (AEs) in electronic diaries up to 7 days following each administered vaccination, as well as through laboratory safety tests, physical examinations and vital signs performed at the study visits. The safety assessments at the study visits cover both the mother and the baby.

AEs in the mother are assessed from the time the informed consent is signed until Day 84. 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 are assessed.

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.

For the babies, all AEs will be assessed for the first 28 days of life, after this only MAAEs, AESIs e.g., GBS disease, abnormal development according to developmental milestones, or SAEs.

For further details, see Table 2 for mothers, and Table 3 for babies.

AEs with onset before the first administration of investigational product in a subject are defined non-treatment emergent AEs, and AEs with onset after the first administration of investigational product are defined treatment emergent AEs.

4.3.3.1 Diaries

The subject will get access to an electronic diary (eDiary) at the study visit where vaccine/placebo is administered. In the eDiary, details of solicited local and systemic reactions will be recorded, for 7 days after each of the vaccinations (the day of the vaccination and the following 6 days).

For solicited local injection site reactions (*redness, swelling, pain, tenderness, itching*) and *pyrexia* (oral temperature >37.9 °C), the diameters and temperatures will be measured, by use of rulers and thermometers, and recorded in the eDiary.

For solicited systemic reactions (*nausea, vomiting, diarrhoea, headache, fatigue, myalgia*), intensities (*mild, moderate*, or *severe*) will be recorded in the eDiary. In addition, other AEs, i.e., unsolicited AEs, including MAAEs, SAEs, concomitant medication (CM) or vaccines will also be recorded and assessed in the eDiary.

The solicited local and systemic reactions, recorded in the eDiary, will be assessed by the site staff.

If serious, the SAEs will undergo evaluation as per the current reference safety information of the IB, as described in section 6.

Details on *new medical problems* (unsolicited AEs), *visits to a doctor* (MAAEs) *or visits to a hospital* (SAEs) or *new medication* (CM) recorded in the diary will be assessed by the investigator at the visits 28 days following each vaccination, as described in section 6.

4.3.3.2 Safety laboratory tests

Safety laboratory testing for all subjects (mothers) will be performed at screening, 4±1 and 28 days after the vaccinations and on Day 84, the last pre-delivery visit. If a participant delivers after Day 0, but before completing all pre-delivery visits, additional safety laboratory tests will be taken at delivery. There is urinalysis (specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrites) at screening, all vaccination visits, at delivery and 28 days post-delivery. If the urinalysis ‘dipstick’ test result is positive for nitrite and/or 2+ or more reported for protein, blood, and/or leucocytes, then urine microscopy and/or culture will be performed.

The results of the safety laboratory testing, and urinalysis will be assessed, and abnormal results will be classified as clinically significant (CS) or not clinically significant (NCS). CS results will be reported as AEs or SAEs, if the criteria for seriousness are met, please see Section 6.1.

The safety laboratory tests in this study are:

Haematology:
Red blood cell count, haemoglobin, haematocrit, platelet count, MCV, MCHC, white blood cell count with absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) counts

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

4.3.3.3 Physical examinations and vital signs in mothers and babies

As part of the safety assessments, for the mothers, there is a full physical examination (respiratory, cardiovascular, gastrointestinal, gross central nervous system, gross musculoskeletal) at screening and at 6 months post-delivery, and targeted physical examinations (respiratory, cardiovascular) before each administration of vaccine, and 28 days post-delivery.

Obstetric examinations [fundal height (no fundal height at visits 2, 4 and 6), foetal movement and foetal heart rate] is performed at all pre-delivery visits for mothers.

Vital signs (heart rate, blood pressure and oral temperature) are measured at all study visits for mothers. At the study visits where vaccine is administered, the vital signs are measured before the vaccination and again 30 minutes post-vaccination prior to leaving the site.

At all vaccination visits the injection sites will be inspected and assessed by the site staff before the subject leaves the site. Photographs may be taken, as required to document unexpected reactions.

In case of identification of a new medical condition (or an increase in intensity/frequency of a condition existing at screening) in the mothers, these will be recorded as AEs, as specified in Table 2.

At birth babies are physically examined and weight, length, head circumference and Apgar score at 1, 5 and 10 minutes, as available, are measured. The babies are physically examined at all baby study visits, as specified in Table 3.

In addition to physical examinations, baby assessments include developmental milestones (age-appropriate developmental milestone checks) and vital signs (heart rate), at all baby study visits after birth, assessing the safety and wellbeing of the babies. If medical conditions are identified in the babies, these will be recorded as AEs, as specified in Table 3.

4.3.4 Immunogenicity assessments

In this study the immunogenicity assessments are both related to the study participants (the mothers) and to their babies. In the mothers, pre-specified vaccine induced immune response markers are measured, whereas in the babies, the same immune markers, obtained through passive transport from the mothers to the babies, are measured.

Quantitative ELISAs are used for detection of IgG specific to the AlpN proteins (RibN, Alp1N, Alp2/3N or AlpCN) and IgG specific to the vaccine fusion proteins (GBS-NN and GBS-NN2) in serum samples, using a calibrated reference standard produced from pooled selected sera from previous studies with GBS-NN and GBS-NN/NN2 which contains IgG specific to the individual AlpN domains and the fusion proteins.

In the primary immunogenicity analysis, concentrations of IgG antibodies, specific to the AlpN proteins from cord blood samples taken at delivery/birth are evaluated and compared between the groups, through calculations of geometric mean concentrations and proportions of subjects with IgG concentrations above the pre-defined thresholds.

The secondary immunogenicity measurements of IgG from maternal blood samples taken at 4 weeks after each vaccination and at delivery are evaluated and compared, including calculation and evaluation of ratios of IgG antibody concentrations between maternal and cord/baby blood at delivery.

IgG measurements from infant blood samples taken at 28 days and 3 months of age, are used for calculation of geometric mean concentrations and proportions of babies with IgG concentrations above pre-defined thresholds as part of the secondary immunogenicity analysis.

[redacted]

4.4 Collection and handling of biological samples

The procedures for taking blood samples from the mothers and the babies will follow standard procedures at the investigational sites. The anticipated total amount of blood taken from the mothers during the study period of approximately 5 months until delivery is up to approximately 10 + 105 + 100 = 215 mL, please see Table 4, where the total amount of blood taken from the babies will not exceed approximately 20 mL, during their first 3 months of life.

For the babies the target blood volumes for the immunogenicity samples are as follows: 5 mL for cord blood, 2 mL for venous blood and 0.5 mL for heel prick blood. Whenever possible cord blood should be taken, venous blood has second priority followed by heel prick blood.

Table 4 Number of tests, volumes of blood per test and total volume of blood for mothers

	Number of tests	Volume of blood per test, mL	Total blood volume, mL
Biochemistry	7	10	70
Haematology	7	5	35
Hep B, Hep C, HIV and syphilis	1	10	10
Immunogenicity	5	20	100
Total blood volume, mL			215

The procedures for taking blood samples from the mothers and the babies, processing, storage, and shipment of biological samples to internal and external laboratories, will, be described in more detail in a study specific laboratory manual.

4.5 Laboratories safety and immunogenicity

The safety laboratory tests will be performed at accredited laboratories, and assessments of the results will be in accordance with current normal ranges, and these will be updated during the course of the study, if applicable.

The ELISAs for detection of IgG specific to the four AlpN domains (RibN, AlpCN, Alp1N, Alp2/3N), i.e., the primary and secondary immunogenicity laboratory analysis, will be validated and performed according to good clinical practice for laboratories.

[redacted]

4.5.1 Biobanking

Only biological samples, where written informed consent to storage in a biobank (after completion of the laboratory analysis included in the protocol), has been obtained from the study subjects, may be transferred to a biobank. Biobank procedures will be in accordance with applicable general data protection regulations (GDPR).

All biological samples are pseudonymised at all times and are not labelled with information which can be used to reveal the identity of the subject, unless access is obtained to the non-pseudonymised data kept at the trial site under the responsibility of the PI(s).

The biological samples taken for safety laboratory analysis specified in this protocol are destroyed after completed analysis.

For the biological samples taken for the immunogenicity laboratory analysis, remaining sample will be transferred to a biobank, after the laboratory analysis specified in the protocol have been completed, if informed consent has been obtained from the subject. The biological samples in the biobank will be used for future immunological research.

4.6 Study population

4.6.1 Overall description of study subjects

A total of 270 pregnant women are planned to be randomised. Sixty participants are assigned to Groups 1 to 3 where the 3 different, two-dose vaccination regimens of GBS-NN/NN2 are administered, 60 participants are assigned to a single dose of GBS-NN/NN2 (Group 4) and 30 participants assigned to three doses of placebo (saline) (Group 5).

Pregnant women, over the legally defined age of consent, carrying a normal singleton pregnancy and is at the planned time of the 1st vaccination, will be recruited from antenatal clinics, connected to the investigational sites, if expected to be available for the scheduled clinic visits for the duration of the study, agree to be contacted by telephone during study participation, and are willing to give parental consent for their baby to participate in the study.

Women may also be identified via a mailout according to local arrangements. One way to identify eligible women will be from hospital lists of patients due to attend for antenatal care.

Potential participants may be approached regarding the study at routine antenatal visits where the pregnant women will be informed about the study.

The rationale for including a pregnant study population, is that the GBS-NN/NN2 investigational vaccine is targeted for vaccination of pregnant women, aiming at passive immunization of their babies with the antibodies generated by the mother, to provide protection of the baby against invasive GBS disease during the first three months of life.

Each woman will, after a screening period of up to 2 weeks, be in the study for approximately 18 weeks (4 ½ months) from 22 weeks GA until delivery, followed by an additional 6 month's post-delivery follow-up period, with safety and immunogenicity assessments for mothers and babies, please see Table 1, Table 2 and Table 3. Taking visit windows into account the study duration for each woman is up to approximately 1 year.

4.6.2 Inclusion criteria

1. Healthy pregnant woman above the legally defined age of consent at the time of screening
2. Carrying a normal singleton pregnancy, and is at 21+0 to 23+6 weeks GA at the planned time of the 1st vaccination, as established by first/second trimester ultrasound examination.
3. Properly informed about the study and has given written informed consent and parental consent (for her baby) in accordance with ICH GCP and local legislation prior to the first study intervention

4. Grants access to her own and her baby's study related medical records

4.6.3 Exclusion criteria

1. Previous vaccination with an investigational Group B Streptococcus (GBS) Vaccine
2. BMI of <17 or >40 at the time of screening
3. HIV, HBV and/or HCV positive or positive for syphilis
4. Knowingly carrying, at screening, a malformed or genetically abnormal foetus, incl. renal pelvis dilation, single umbilical artery (screening will be undertaken after the ultrasound conducted for the detection of anomalies)
5. Chronic or pregnancy induced hypertension at screening, >1+ protein in urine regardless of blood pressure or 1+ protein in urine and hypertension
6. Experienced a previous stillbirth prior to going into labour
7. Gestational, type 1 or type 2 diabetes
8. Potential placenta previa as per malformation ultrasound scan
9. Rhesus negative and has anti-D antibodies or other potential harmful antibodies
10. Known or suspected allergies to any components of the vaccine including to aluminium or aminoglycoside antibiotics, or an allergic reaction related to a previous vaccination
11. Fever (temperature >37.9°C) on the day of receiving the first dose or an acute infection in the 7 days before the first dose (the first dose can be delayed if gestational age permits)
12. Received systemic steroids in the 6 weeks before the first dose (inhaled and topical steroids are acceptable)
13. Any lesion (including tattoos) at the planned injection site that will impair the assessment of the injection site
14. Received immunosuppressive medication, chemotherapy or radiotherapy in the 24 weeks before the first dose
15. Received blood, blood products, plasma derivatives or any immunoglobulin preparations in the 12 weeks before the first dose
16. Anaemia, haemoglobin (<10 g/dL, 100 g/L, 6.2 mmol/L)
17. Currently breast feeding
18. Received any investigational medicinal product or vaccine in the 12 weeks or 5 half-lives before the first dose
19. Received an approved vaccine within the 4 weeks before the first dose or expects to receive an approved vaccine during the study. Routine vaccinations recommended during pregnancy (e.g., pertussis and influenza) are permitted but every effort should be made to separate routine vaccinations from the trial vaccinations by at least 7 days.

20. Known or suspected immunodeficiency or cancer (leukaemia, lymphoma), or a family history of congenital or hereditary immunodeficiency
21. History or presence of uncontrolled cardiovascular disease, pulmonary, hepatic, gall bladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, or autoimmune disease
22. History of, or current drug or alcohol abuse
23. In the opinion of the investigator not suitable for inclusion in the study
24. The pregnancy is considered high risk by treating physicians

4.7 Discontinuation of subjects and treatment

A subject may be discontinued from therapy (i.e., not receive her second dose), but remain in the study for follow-up, for safety and immunogenicity study endpoints, if applicable, in the opinion of the investigator.

4.7.1 Subject discontinuation (individual subject)

A subject is free to leave the study any time without giving a reason, according to the Declaration of Helsinki.

Although a subject is not obliged to provide reason(s) for withdrawing consent, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

If the reasons are obtained, the primary reason for withdrawing consent must be specified in the end-of-study form in the eCRF.

The investigator may withdraw an individual subject from the study in case of an adverse event that, in the opinion of the investigator, precludes any further participation in the study, the primary reason for the investigator's decision, must be specified in the end-of-study form in the eCRF.

4.7.2 Treatment discontinuation (individual subject)

Discontinuation of study treatment is not the same as withdrawal from the study. If vaccination is stopped for an individual subject, the subject may stay in the study to perform scheduled assessments, if applicable, in the opinion of the investigator.

A permanent contraindication (stopping rule) is defined as an adverse event experienced by a study subject that leads to the conclusion that no investigational product can be administered to the study subject anymore, i.e., withdrawal from administration of the investigational product.

The investigator must permanently stop vaccination of an individual subject in case of:

- An objective clinical or laboratory parameter change which by the investigator is assessed as severe in intensity AND is judged to be related to the investigational product

- An AE thought to be an allergic reaction to the investigational product, including anaphylaxis, bronchospasm, perioral oedema, extensive rash (>40% body surface), urticaria, generalized petechiae, or erythema multiforme judged to be related to the investigational product
- Temperature >38.9 °C within 72 hours after a vaccination, for no apparent reason
- Any event that in the opinion of the investigator precludes administration of any further investigational product

For solicited local or systemic reactions reported and rated by the subjects in the eDiary, it is at the investigator's discretion to assess if the individual subject should be withdrawn from study treatment, according to the criteria above.

Subjects withdrawn from the study within 6 months after the last product administration, will be contacted at least 6 months after the last product administration for recording of SAEs and AEs of special interest.

A temporary contraindication (pausing rule) is defined as an event experienced by a study subject that leads to the conclusion that no investigational product can be administered to the study subject until the event has resolved.

The investigator must postpone the vaccination of an individual subject in case of:

- Acute infection in the 7 days before the vaccination or treated for acute infection with antipyretics/analgesics in the 24 hours before the vaccination
- Elevated temperature measured prior to the vaccination (> 37.9 °C)

The vaccination is postponed until 7 days after the acute infection has resolved, the antipyretics/analgesics treatment has ceased for 24 hours and/or the temperature is ≤ 37.9 °C.

4.7.3 Lost to follow-up

Validity of the study is a potential issue when subjects are lost to follow-up, as information that is important to the endpoint evaluation is then lost. Subjects are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures.

A subject will be considered lost to follow-up if she fails to return for a scheduled visit and cannot be contacted or reached by the study site staff after 3 attempts.

Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls, letter or e-mail) to the subject's last known number or address. These contact attempts will be documented in the subject's medical records.

Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.7.4 Replacement of study subjects

Subjects allocated a randomisation number, who are discontinuing the study for any reason before the receipt of an injection/dose, will be replaced by new subjects.

Subjects receiving at least one injection/dose who are discontinuing the study early will not be replaced by new subjects.

4.8 Temporarily halt or early termination of the clinical study

The whole study may be temporarily halted or terminated early.

If the investigator, the sponsor, the safety medical monitor or the DSMB becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be temporarily halted or terminated early after appropriate consultation between the relevant parties, see Section 6.8.

The study may also be temporarily halted or terminated early at the sponsor's discretion in the absence of such a finding, for example due to failure to enrol subjects at an acceptable rate, or a decision on the part of the sponsor to suspend or discontinue development of the investigational product.

If the clinical study is temporarily halted or terminated early, the independent ethics committee (IEC) and competent authority (CA) will be notified, as applicable, see Section 0.

4.9 Start and end definitions and duration of study

The start of the study is the first visit of the first participant and the end of the study is the time of obtaining the laboratory analysis results for the primary and secondary immunogenicity analysis.

An individual participant will be in screening for up to 2 weeks and included in the study for approximately 18 weeks (4 ½ months) from 22 weeks GA until delivery, plus an additional 6 month's post-delivery follow-up period, which, taking post-delivery visit windows into account adds up to a total study duration of up to approximately 1 year.

5 Investigational products

The investigational products will only be administered to participants included in this study and only according to the procedures described in this protocol.

Only the unblinded study team members (incl. site staff and monitor), may handle/check and have access to the investigational products and will be responsible for procedures for receipt, storage, and monitoring of storage conditions of the investigational vaccine/placebo, and for the assembly, dispensing and injection of vaccine/placebo in the study. Alternatively, the actual injection of vaccine/placebo may be performed by blinded study team members by use of syringes with opaque tape, to avoid unblinding during the injections.

5.1 Identity and description of the investigational vaccine

The vaccine antigen, "(NN+NN2) DP", is a *clear, colourless to slightly yellow* sterile solution for injection, filled into vials. The vaccine adjuvant, Alhydrogel®, is a *white to slightly yellow uniform cloudy white suspension which may sediment during storage* sterile suspension for injection, filled into vials.

Table 5 Antigen and adjuvant components delivered to the sites

Product Name	Strength	Form
"(NN+NN2) DP" (antigen)	0.7 mg/mL (+/- 10%): 0.35 mg/mL GBS-NN 0.35 mg/mL GBS-NN2	Sterile solution for injection (2.5 mL)
Alhydrogel® (adjuvant)	1.4 mg/mL Al3+ ion	Sterile suspension for injection (0.5 mL)

5.2 Assembly of the investigational vaccine at the site

The investigational vaccine (GBS-NN/NN2) will be delivered to the sites as two separate components: "(NN+NN2) DP" and Alhydrogel®, to be assembled at the site pharmacy, or alternatively by unblinded, appropriately trained nursing staff:

- "(NN+NN2) DP": 0.7 mg/mL (+/- 10%) with 0.35 mg/mL GBS-NN and 0.35 mg/mL GBS-NN2. Each vial contains 2.5 mL
- Alhydrogel®: 1.4 mg/mL Al3+ ion. Each vial contains 0.5 mL

The investigational vaccine will be assembled, locally at the site pharmacy, by adding a volume of 0.2 mL of the "(NN+NN2) DP" (after thawing) to the vial with 0.5 mL of Alhydrogel®.

The assembled investigational vaccine (GBS-NN/NN2), is a sterile suspension for injection, which contains 50 µg of the two vaccine fusion proteins NN and NN2 and 0.5 mg of aluminium per 0.5 mL.

The information in this section will be described in more detail in a study specific pharmacy manual.

Please refer to the investigator's brochure for more detailed information on the investigational products.

5.3 Dosing and administration of investigational and placebo vaccines

The study vaccines may only be administered by authorised staff as indicated in the investigational site signature and delegation form.

For all groups in the study, and for investigational product, as well as placebo (saline), a dose of 0.5 mL sterile suspension (investigational vaccine) or solution (saline) for injection, is injected intramuscularly into the deltoid muscle, preferably of the non-dominant arm, at each dosing occasion.

Each vial and box of investigational vaccine and placebo (saline) are labelled, indicating the type of product, and thus the identity of the product (investigational vaccine / placebo) will be known to the unblinded site staff responsible for dispensing and injection procedures and maintenance of the related records, as well as to the unblinded monitor, checking these procedures and records.

The unblinded site staff and the unblinded monitor will not reveal the identity of the injected vaccine/placebo to any blinded study team member, including the blinded site staff, responsible for the safety assessments, and the blinded monitor. For more details on blinding and breaking the blind, please see Section 5.6.

The blinded study team members will verify eligibility for vaccination (per Sections 4.6.2 and 4.6.3 or 4.7.2, as applicable, depending on 1st, 2nd or 3rd dose) including measuring pre-vaccination vital signs, and will refer the subject to vaccination, to be performed by the unblinded study team members, or alternatively by blinded study team members, by use of syringes with opaque tape, to avoid unblinding during the injections.

Administration of investigational vaccine / placebo:

- Check that the shelf-life of 24 hours for the assembled investigational vaccine has not expired and check the participant number on the label of the vial, see Section 5.7.2.
- Invert the vial gently prior to drawing up the suspension / solution with a sterile disposable syringe fitted with a needle
- Draw up 0.5 mL of investigational vaccine / placebo (saline) for administration
- Injections must be given deeply intramuscularly, preferably in the subject's non-dominant arm in the deltoid muscle. The dominant arm may be used if it is not possible to administer into the non-dominant arm (e.g., due to an ongoing injection site reaction, or a tattoo making assessment of the injection site difficult)
- The empty vials including boxes are kept at the investigational site, or similar local procedure according to GCP, for drug accountability. They must be kept in a secure place and may only be accessed by the unblinded site staff and the unblinded monitor

– Dispensing and administration details are recorded in relevant study documents/logs and in the eCRF according to instructions

All study subjects must stay at the investigational site for at least 30 minutes after each injection, due to the potential risk of immediate AEs.

Before the study subject leaves, the blinded site staff must inspect the injection site, measure and record vital signs, and document the occurrence of any AEs in the first 30 minutes, or that no AEs occurred in the first 30 minutes.

The information in this section will be described in more detail in a study specific pharmacy manual.

5.4 Precautions and overdosing

Acute anaphylactic reactions are very rare when administering vaccines. However, the necessary equipment and medication for treatment of an anaphylactic reaction must always be in place when administering vaccines, such as resuscitation equipment and medication.

A maximum tolerated dose in humans has not been determined and no data exist on the effects of overdose with GBS-NN/NN2. The highest dose of GBS-NN administered was 250 µg in a previous clinical study (MVX13211).

However, as the vaccine is administered by the study team under controlled conditions, an overdose is unlikely. If an overdose does occur symptomatic treatment should be initiated along with general supportive care.

5.5 Randomisation and assignment of subjects to treatment

The randomisation list will be prepared by a statistician who will not, in any way, participate in the data management or the statistical analysis of the data from the clinical study before the database has been released for analysis.

The randomisation list will be generated by a validated SAS program and kept in a restricted access folder and will subsequently be integrated in the eCRF.

The randomisation (i.e., group assignment) of a new subject at the investigational sites will take place using the eCRF. Only unblinded site staff and the unblinded monitor have access to the unblinded randomisation module. Unblinded study team members may not reveal any unblinded information to any blinded study team members and must keep the unblinded randomisation documents in a secure place.

A sequence of participant screening numbers will be allocated to each site, and these numbers will be assigned to the subjects who enter screening, i.e., the randomisation will be stratified on site. When a subject has completed screening and is eligible for inclusion, the blinded site staff will randomise the subject in the randomisation module in the eCRF and a randomisation number will be generated. The blinded site staff will only be able to see randomisation date, time and randomisation number in the randomisation module. The unblinded information will be hidden for all blinded staff. Once the subject has been assigned a randomisation number an automated alert

email will be sent to the relevant unblinded site staff responsible for dispensing and injecting vaccine, and the vaccine for the subject will be prepared and injected according to the information in the unblinded randomisation module in the eCRF.

5.6 Blinding and breaking the blind

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 will, if applicable, be described in more detail in a study specific blinding manual.

5.7 Packaging, labelling and storage

The investigational products, i.e., the antigen and adjuvant components delivered to the sites, are filled, packaged, and labelled (inner and outer packaging) at Biovian Ltd, Tykistökatu 6B, Biocity 20520 Turku, Finland, according to good manufacturing practices (GMP).

5.7.1 Packaging and labelling

The labels for inner and outer packaging are in compliance with relevant legislation.

The vaccine antigen and adjuvant may not be used after the indicated use by dates.

The information in this section will be described in more detail in a study specific pharmacy manual.

5.7.2 Product storage, stability, shelf-life and thawing

The investigational products must be kept in a safe place at the study site, under the responsibility of the site PI and/or at a central storage under the responsibility of a pharmacist.

The antigen, “(NN+NN2) DP”, should be stored in a freezer at -20°C±5°C (-25°C to -15°C).

The adjuvant, Alhydrogel®, should be stored in a refrigerator at + 2°C to + 8°C. Alhydrogel **must not** be frozen.

The placebo (0.9 % saline sterile solution for injection) should be stored according to the manufacturer's instructions.

The freezer(s) and refrigerator(s) used for storage of the investigational products must be temperature monitored with storage temperatures being recorded in storage condition monitoring logs.

The investigational products as well as the placebo will be kept under the required storage conditions and the records will be verified by the unblinded monitor.

In case of deviations in storage conditions of the investigational products, the affected product may not be used, and the relevant person at MinervaX must be contacted, in order to decide, if the product should be discarded and replaced, or if continued use can be allowed.

The vaccine antigen, "(NN+NN2) DP", must thaw at room temperature for up to 2 hours, or in the refrigerator at + 2°C to + 8°C overnight, prior to the start of the assembly process described in Section 5.2.

The assembled investigational vaccine has a shelf-life of 24 hours from the time of inserting the needle in the vial of the vaccine antigen, "(NN+NN2) DP".

Similarly, it will be defined for the placebo that the time from inserting the needle (to draw up the saline) until injection of the placebo into the subject, must not exceed 24 hours.

The information in this section will be described in more detail in a study specific pharmacy manual.

5.7.3 Transport procedures for investigational products

The investigational products (DPs) will be released by a qualified person (QP) and subsequently transported to the investigational sites when the clinical study has been approved by the relevant CA and the IEC, i.e., regulatory green light (RGL) is in place.

The transport of the products (DPs) will be arranged maintaining the cold chain, in compliance with the required temperatures, for the antigen, "(NN+NN2) DP" -20°C±5°C (-25°C to -15°C), dry ice should not be used, and for the adjuvant, Alhydrogel® (+ 2°C to + 8°C).

It is considered a critical violation if the adjuvant is exposed to freezing.

Temperature loggers will be used for monitoring of the storage conditions during the transport.

Procedures will be in place for documenting the dispatch of the investigational products from the manufacturer and the receipt of the products at the investigational site.

During the clinical study, the unblinded monitor will check that the dispatch/receipt documentation in the investigator's file is adequate and correct.

The information in this section will be described in more detail in a study specific pharmacy manual.

5.8 Treatment compliance procedures

The IMP is administered by health care professionals; therefore, participant compliance with dosing will not be an issue. During the clinical study, the unblinded monitor will check vaccine administration documentation to check that vaccines are administered correctly.

5.9 Investigational product accountability procedures

The empty vials and boxes are kept in a secure area at the investigational site for drug accountability, or similar local procedure according to GCP. The secure area may only be accessed by the unblinded site staff responsible for dispensing/injecting the vaccines and by the unblinded monitor.

The study vaccines will not be destroyed until destruction is approved by the sponsor after completion of the final accountability has been confirmed by the unblinded monitor.

A GCP destruction certificate will be issued to document completed destruction and will be filed in the TMF.

5.10 Concomitant medications and vaccines

All mothers will receive intrapartum antibiotic prophylaxis (IAP) if clinically indicated. Should any babies develop a GBS infection over the course of the study they will be treated by the hospital's standard of care protocol for such infections.

5.10.1 Recording of previous and concomitant medications and vaccines

Prior and concomitant medications (CMs) or vaccines are to be recorded in the eCRF including over-the-counter medications and supplements.

Concomitant medication is any medication or vaccine apart from the investigational vaccine and placebo that the subject receives while participating in the study. The investigator or delegate must seek information on CM use, as specified for the individual study visits as per Table 2 and Table 3. The information collected for CM must include:

- Medication name (preferably generic name)
- Indication
- Dosage
- Frequency
- Route of administration
- Start and stop date or ongoing

5.10.2 Prohibited previous and concomitant medications and vaccines

The following concomitant medications should be avoided during the study:

- Systemic steroids (inhaled and topical steroids are acceptable)
- Immunosuppressive medication, chemotherapy or radiotherapy
- Blood, blood products, plasma derivatives or any immunoglobulin preparations
- Other investigational medicinal products or vaccines

The following concomitant vaccines should preferably be administered with an interval of 7 days (before or after) the study vaccinations:

- Routine vaccinations recommended during pregnancy (e.g., pertussis and influenza), Covid-19 vaccine, or other indicated vaccines

6 Safety procedures

This section of the protocol defines periodic and expedited adverse event (AE) reporting obligations of the investigators.

Definitions and terms follow ICH E6 (R2) and Directive 2001/20/EC (to be replaced by Regulation (EU) 536/2014 when implemented).

In this study, adverse events (AEs) will be collected from the time of signing the informed consent form. AEs with onset prior to the first administration of GBS-NN/NN2 or placebo, will be designated non-treatment-emergent AEs where AEs with onset after the first administration of vaccine will be designated treatment emergent AEs.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or serious adverse event (SAE), as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for reporting AEs and SAEs.

The information in this section will, if applicable, be described in more detail in a study specific pharmacovigilance management plan.

6.1 Adverse events definitions and terms

Adverse Event (AE):
Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the investigational product.

The AE will be described in precise, standard medical terminology (i.e., not necessarily the exact words used by the subject). If known, a specific diagnosis should be stated.

Serious Adverse Event (SAE):
An AE that at any dose:

- Results in death; **Fatal**
- Is **Life-threatening***
- Requires inpatient **Hospitalisation or prolongation of existing hospitalisation**
- Results in **Persistent or significant disability or incapacity**
- Results in **Congenital anomaly or birth defect**
- Is **Medically important**

*The term ‘life-threatening’ refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it had been more severe.

Scheduled hospitalisation periods that were planned before the subject was included in this study are not to be considered serious.

In order to evaluate the risk of the IMP to cause severe liver injury the following must always be reported as a SAE under the criterion important medical event: Any occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN and confirmed as a Hy's Law case.

Hy's Law:
AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, where no other reason (i.e., viral hepatitis), other than the study intervention, can be found to explain the combination of increases.

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Medically important events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation.

Admissions to hospital for a normal birth or for an elective Caesarean section leading to a healthy, term birth will not be deemed a serious adverse event, unless deemed an emergency caesarean section, in which case the reason the Emergency Lower Segment Caesarean Section (LSCS) was required will be reported as SAE.

Clinical laboratory abnormalities and other abnormal assessments as AEs or SAEs:

Abnormal laboratory findings (e.g., clinical chemistry, haematology, and urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they also meet the definition of a SAE.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen (in intensity or frequency) following the start of the study will be reported as AEs or SAEs.

A pre-existing condition (i.e., a disorder present before the AE reporting started and noted on the medical history/physical examination form) should not be reported as an AE unless the condition worsens (in intensity or frequency) during the AE reporting period.

The reasonable suspected **causal relationship** of an AE to an investigational product is assessed using the following terms:

Reasonable possibility of being related
An event for which, after careful medical evaluation, a connection with trial medication cannot be ruled out with certainty. The event occurs after exposure to trial medication. The event may occur at a reasonable time in relation to the time of administration of the trial medication but might also be attributable to a commonly occurring alternative cause. Alternatively, the event may not occur at a reasonable time in relation to the time of administration of trial medication but may not be attributable to an alternative cause.

No reasonable possibility of being related
An event which occurs before exposure to the trial medication, or which does not occur at a reasonable time in relation to the time of administration of trial medication and can be attributed to a commonly occurring alternative cause. Alternatively, the event is unrelated to the trial (e.g., road traffic accident), unless it can be demonstrated that the treatment could have caused the event.

Adverse Reaction:
An AE assessed as related (reasonable possibility of being related) to the investigational product administration. All injection site events are defined as related to the investigational product.

Suspected Unexpected Serious Adverse Reaction (SUSAR):
A serious adverse reaction where the nature, intensity, frequency or outcome is not consistent with the information in the reference safety information, in the investigator's brochure or the summary of product characteristics. A SUSAR is serious, related and unexpected.

All SAEs may be regarded as SUSARs, depending on the applicable reference safety information.

The **intensity** of an AE is assessed using the following terms:

- **Mild** – no interference with subject's daily activity, easily tolerated (grade 1)
- **Moderate** – moderate interference with subject's daily activity may require intervention (grade 2)
- **Severe** – considerable interference with / prevention of subject's daily activity requires intervention (grade 3)

In addition, "Guidance for Industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials, US Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research, September 2007"will form the basis of the rating (mild, moderate, severe) of solicited injection site reactions (*redness, swelling, pain, tenderness)*, and *pyrexia* (oral temperature >37.9 °C), where the diameters and temperatures will be measured by the subjects and recorded in electronic diaries, as well as for the rating of solicited general reactions of *nausea, vomiting, diarrhoea, headache, fatigue and myalgia.*

The **outcome** of an AE is assessed using the following terms:

- **Recovered/resolved**
- **Recovering/resolving**
- **Not recovered/not resolved**
- **Recovered/resolved with sequelae**
- **Fatal**
- **Unknown**

6.2 Follow-up of adverse events

All AEs, irrespective of the seriousness or causality, will be followed until the event has recovered/resolved or is considered stable, any abnormal laboratory values have returned to baseline or stabilised at a level acceptable to the investigator and safety medical monitor, until there is a satisfactory explanation for the change observed, or until the subject is lost to follow-up.

6.3 Medically attended adverse events (MAAEs) and adverse events of special interest (AESIs)

A medically attended adverse event (MAAE) is an AE that leads to an unscheduled visit to a health care person.

For this study adverse events of special interest (AESI) are GBS disease, autoimmune diseases and immune-mediated reactions in the mothers, and GBS disease and abnormal development according to developmental milestones in the babies. AESIs will be reported separately to SAEs, from the day of signing the informed consent, and until the end of the study (Visit 11).

For infections that could potentially be caused by GBS (e.g., urinary tract infections in mothers or neonatal sepsis in babies), the sites should follow their standard procedures to identify the causative organism.

6.4 Reporting of adverse events including SAEs, MAAEs and AESIs

AEs will be reported in the eCRF pages from informed consent until the subject has completed/is withdrawn from the study (including any follow-up period), see details in Table 2 for mothers and Table 3 for babies.

Adverse events identified from the e-diaries will be transferred to the AE form in the eCRF, if they meet the following criteria:

- Any unsolicited AE
- Solicited local or systemic reaction to be assessed for the subject's withdrawal from study or study vaccine
- Solicited local or systemic reaction, rated by the subjects in the eDiary, categorized as severe
- Solicited local or systemic reaction lasting beyond 7 days from the day of vaccination
- Solicited local or systemic reaction that meets the definition of a SAE

Solicited local or systemic reactions are per definition regarded as related to the study vaccine, and the intensity is defined as described in section 6.1.

All maternal SAEs, as well as medically attended adverse events (MAAEs) and AEs of special interest (e.g., GBS disease, autoimmune diseases and immune-mediated reactions) will be reported from the day of signing informed consent for study participation and until the end of the study (Visit 11).

All baby SAEs, as well as MAAEs and AESIs (e.g., GBS disease, abnormal development according to developmental milestones), will be reported from birth up to 180 days post-delivery (Visit 11).

All SAEs, and AESIs, occurring from the time of signing the informed consent form until the subject has completed the study will be reported by completing and sending the SAE form (via email, or if required, via fax) to the pharmacovigilance provider (contact details below) within 24 hours of awareness / learning about the event i.e., within 24 hours after the investigator becomes aware that the event meets the protocol definition of a SAE.

SAEs occurring after study termination must be reported if considered related to the study drug.

After the initial SAE report, the investigator is required, proactively, to provide further information regarding the subject's condition.

In case of a fatal or life-threatening suspected unexpected serious adverse reaction (SUSAR), relevant follow-up information should be forwarded immediately.

6.5 Sponsor's expedited reporting of SAEs and SUSARs

Reporting of SAEs and SUSARs to competent authorities and independent ethics committees (IECs) will follow all local and international legal requirements.

After receipt of the SAE report from the investigator, the pharmacovigilance provider ensures expedited reporting to relevant competent authorities (CAs) and IECs (if not done by investigators) and other stakeholders such as investigators in other studies with the same investigational product, as applicable.

The contact details of the phamacovigilance provider are as follows:
Diamond PV Services Limited
Suite 2, Ground Floor
Field House
Station Approach, Harlow
Essex CM20 2FB, UK
Tel: +44 (0) 1279 4076 759
Fax: +44 (0) 1279 418 964
Email: pvservices@diamondpharmaservices.com

Expedited reporting to CAs and IECs is normally only required for SUSARs. The expedited reporting timelines are:

- For SUSARs resulting in death or life-threatening events, notification should be given no later than 7 days after sponsor's first knowledge of the event. The completed expedited reporting form should be available to the CA and IECs after an additional 8 calendar days

- For other SUSARs, the completed expedited reporting form should be available to the CA and IECs no later than 15 calendar days after the sponsor's first knowledge of the event (notification prior to this is not required)

6.6 Sponsor's periodic reporting of SAEs and SUSARs

The sponsor's and/or the pharmacovigilance provider's procedures for periodic and annual reporting of SAEs and SUSARs to CA and IECs, including development update safety reports (DSURs) will be in compliance with applicable regulations.

6.7 Data safety monitoring board

A data safety monitoring board (DSMB) comprised by independent experts will advise the coordinating site PIs and the sponsor.

The DSMB will convene for three pre-planned DSMB meetings to review adverse events (AEs) data. The first DSMB meeting will take place when 27 subjects (10 %) have received their 1st injection at 22 weeks GA (on average 12/27 will have received GBS-NN/NN2 and 15/27 placebo) including 28 days post-vaccination AE follow-up. The second DSMB meeting will take place when 27 subjects have given birth including 28 days post-delivery AE follow-up, and finally a third meeting will take place one year after the first subjects first visit (FSFV). The pre-planned DSMB reviews are conducted while the study is still ongoing.

The membership of the DSMB will reflect the disciplines and medical specialties necessary to interpret the data from the clinical study and to fully evaluate participant safety. No member of the DSMB should have direct involvement in the conduct of the study. Furthermore, no member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB.

The members of the DSMB serve in an individual capacity and provide their expertise and recommendations according to a DSMB charter. The primary responsibilities of the DSMB are to: 1) periodically review and evaluate the accumulated study data on safety, study conduct and progress and 2) make recommendations concerning the continuation, modification, or termination of the study. The DSMB considers study specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB advises the sponsor about safety issues and might recommend a temporary halt, early termination or resumption of enrolment based on changes to the protocol that improve the benefit risk balance, after a temporary halt etc. However, it will remain the sponsor's and concerned CA and IECs final decision if study activities are early terminated or resumed after a temporary halt.

6.8 Unexpected events that warrant temporary halt or early termination (study stopping rules)

Safety related events that warrant temporarily halt of the study for data safety monitoring board (DSMB) review or early termination of the study (study stopping rules) include, but are not limited to:

- Occurrence of a SAE following vaccination in one subject for which the investigator determines that the SAE is related to the vaccination

- Anaphylaxis or bronchospasm following vaccination in one subject that is considered at least possibly related to the vaccination
- ≥ 3 subjects up to the first 27 subjects receiving a study injection (approximately the time of the first DSMB review), and then ≥10% of subjects (after >27 subjects injected), have the same or similar severe (grade 3) AEs assessed as having a reasonable possibility of being related to the vaccination

All severe reactions are monitored and will trigger a DSMB meeting according to the criteria listed above. For solicited local or systemic reactions reported and rated by the subjects in the eDiary, it is assessed by the investigator, if the reactions are severe, as per the protocol Section 6.1.

6.9 Sponsor's other reporting obligations relevant for safety

If unexpected information comes to light that affects the benefit risk balance of the clinical study, but is not an adverse event, as referred to above, notification to CA and IEC will be without undue delay, within 15 days from the date the sponsor becomes aware of the information.

Where unexpected information is likely to seriously affect the benefit risk balance, the sponsor and the investigator will as soon as possible take appropriate urgent measures to protect the subjects, and notification about the measures taken will be given to CA and IEC without undue delay, within 7 days from the date the measures were taken.

6.10 Covid-19 Risk Assessment

The principal investigator and sponsor have reviewed the risks of conducting the study in light of the current COVID-19 pandemic. The first priority is the safety of trial subjects and staff, but there is also an ethical duty to preserve the scientific integrity of the study as far as possible.

Currently vaccinations against COVID-19 are not indicated in pregnant women but with trials of COVID vaccines in pregnant women ongoing, this may change. If a participant requires a COVID-19 vaccination every effort should be made to separate the investigational vaccine and the COVID-19 vaccine by at least 7 days. The COVID-19 vaccination should take priority over the investigational vaccine.

No data are available regarding the co-administration of COVID-19 vaccine with GBS-NN/NN2; therefore, this should be avoided. It is considered unlikely that there will be a vaccine-vaccine interaction, but no data are available. It is not considered that there is a significant increase in risk to participants by conducting this study during the pandemic.

Local COVID-19 guidance or restrictions will be followed any time.

7 Data management and statistics

7.1 General considerations

The CRO Larix will be delegated the tasks of data management and statistics.

7.2 Data management

The planned data management procedures will be detailed in the data management plan and related data management documents.

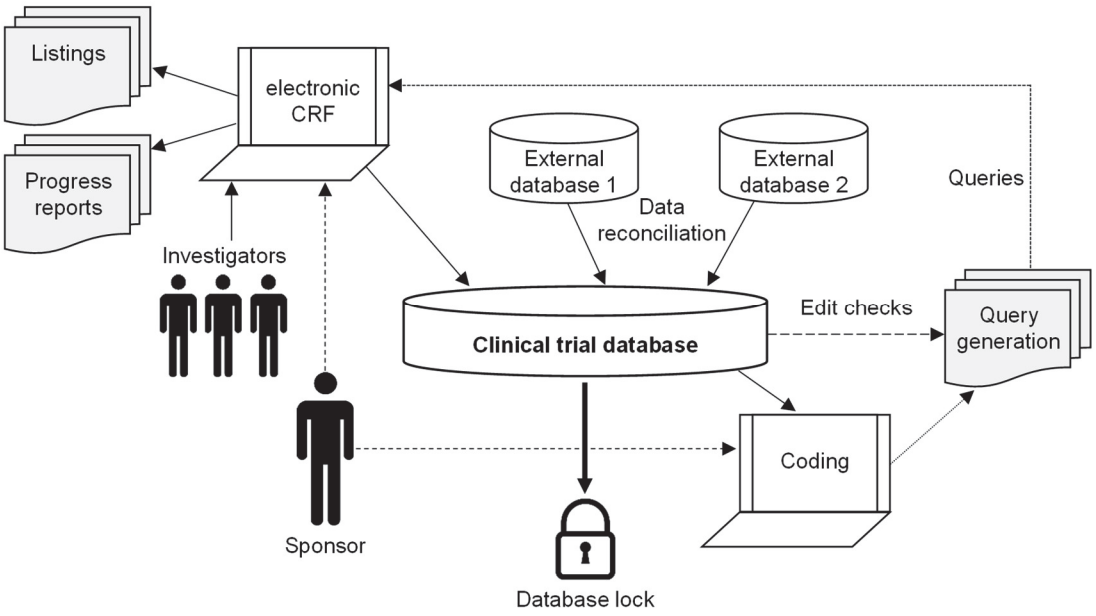
Each participating site will maintain appropriate medical and research records for this study, as per current regulatory and institutional requirements for protection of personal data and confidentiality of the subjects, as well as per ICH GCP E6 (R2) ensuring human subject protection and the data integrity.

Data will be collected by means of Electronic Data Capture (EDC). The investigator or staff authorised by the investigator will enter subject data into eCRFs. Data recorded in the eCRFs will be accessible to site staff and sponsor staff immediately after entry.

Data collection is the responsibility of the site staff under the supervision of the site PI. The site PI is responsible for data integrity i.e., ensuring that data is attributable, legible, contemporaneous, original or a true copy, accurate, complete, consistent, enduring and available (ALCOA+).

Clinical data (including AEs, concomitant medications and solicited adverse reactions data) and clinical laboratory data will be entered into Viedoc™, a 21 CFR Part 11-compliant data capture system provided by the Viedoc Technologies AB. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Figure 1 illustrates the flow of data collected for this study.

Figure 1 Flow of data for study



7.3 Statistics

Details of the planned analyses will be described in the Statistical Analysis Plan (SAP), providing a detailed discussion of the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final clinical study report. The SAP will be finalized before data base release and the subsequent unblinding.

All study data will be listed, and all endpoint data will be tabulated. All categorical data will be tabulated by frequency and percentage while all continuous data will be tabulated by arithmetic mean, standard deviation, and range. Data used for log-transformed analyses will also be tabulated by geometric mean and coefficient of variation. This will be relevant for the immunogenicity endpoints. Exposure to vaccinations and compliance with the vaccination schedule will be tabulated and listed. All statistical analyses will be adjusted by site, as randomisation is stratified.

7.4 Disposition of subjects

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.

7.5 Protocol deviations

All protocol deviations, with classification minor/major, will be presented in a listing and summary table.

The following deviations may be grounds for classification as 'major':

- Deviation to one or more key inclusion/exclusion criteria
- Significant non-compliance with study vaccine administration
- Significant deviation from time windows as defined by a week's (± 7 days) deviation from schedule
- Incorrect/wrong treatment allocation

7.5.1 Significant and serious breaches of the protocol, SOPs or GCP

In case of non-compliance with the protocol, SOPs or ICH GCP E6 (R2) that significantly affects human subject protection or the reliability of the study results, a root cause analysis will be performed, and appropriate corrective and preventive actions will be implemented.

Serious breaches will be reported without undue delay no later than 7 days after the sponsor becomes aware of the breach. Please see Section6.9.

7.6 Analysis populations

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 BIG and BPP sets refer to the children born to study participants.

- Safety analysis set (SAF): All recruited and randomized mothers who receive at least one dose of the study vaccine or placebo
- Maternal Immunogenicity Set (MIG): The subset of SAF 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
- Maternal Per Protocol Set (MPP): The subset of MIG 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 up to delivery (no major protocol violation)
- Baby safety set (BSA): The babies born to mothers who have received at least one dose of the study vaccine or placebo
- Baby Immunogenicity Set (BIG): The babies born to mothers who qualify as members of the MIG analysis set
- Baby Per Protocol Set (BPP): The subset of BIG born to MPP mothers where the baby provides evaluable samples for analysis, either cord or venous blood within 72 hrs of birth

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

7.7 Demographics, baseline characteristics and concomitant medications

Treatment groups are compared as regards baseline characteristics, including demographics, medical history, prior and concomitant medication which will be coded after WHO Drug Dictionary. Medical history will be coded using the latest available version of MedDRA.

7.8 Analysis of immunogenicity (primary endpoint)

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

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

B) Seroprotection as defined by AlpN-specific IgG concentrations being 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 (anticipated to be approximately 18 weeks from administration of first vaccine dose, taking place at the pregnancy's 22 weeks gestational age).

The endpoints will be compared, as described below, between the 5 intervention groups:

- Group 1: 2 doses GBS-NN/NN2 at 26 & 30 weeks GA
  (1st dose given 3rd trimester; 4 weeks interval)
- Group 2: 2 doses GBS-NN/NN2 at 22 & 26 weeks GA
  (1st dose given 2nd trimester; 4 weeks interval)
- Group 3: 2 doses GBS-NN/NN2 at 22 & 30 weeks GA
  (1st dose given 2nd trimester; 8 weeks interval)
- Group 4: 1 dose GBS-NN/NN2 at 26 weeks GA
  (one dose given 3rd trimester)
- Group 5: Placebo at 22, 26 & 30 weeks GA
  (1st placebo dose given 2nd trimester, 4 weeks interval)

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.

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. In general, the attrition rate is expected to be low.

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:

- binary endpoints (seroprotection): 15% points (0.15) on the absolute scale
- for IgG concentrations: here a GMC ratio of 2/3 is considered adequate.

The null hypotheses 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 sero-protection rate, defined by 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.

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.

For the comparison of vaccination groups 1 to 4 with the placebo group 5, the same analysis is applied, but no non-inferiority consideration is applied. Instead, the usual p-values corresponding to superiority testing will be presented together with the estimated differences and a two-sided 90% CI.

Due to the large number of performed tests, these non-inferiority procedures are considered of non-confirmatory nature and no control for multiplicity is applied.

The primary analyses are based on the BIG analysis set and this will form the basis for conclusions. As sensitivity analyses the primary analyses will be repeated on the BPP analysis set.

7.9 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 set):

- 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
- The subject level ratios of antibody concentrations between maternal and cord blood at delivery

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. Possibly allowing for changing variance across visits and visit times group interaction. In this way the ratio of GMCs (GMCR) comparing vaccination groups can be derived.

7.10 Analysis of safety (key secondary endpoint)

7.10.1 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
- Treatment-emergent SAE
- Vaccine related TEAE

- Vaccine related severe TEAE
- Treatment-emergent vaccine related SAE
- TEAE leading to withdrawal
- TEAE with outcome death

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

- Solicited injection site events following the vaccinations
- Solicited systemic AEs following the vaccinations
- All AEs following the vaccinations

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.

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 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

7.10.2 Safety laboratory assessments, urinalysis and vital signs

Treatment groups are compared as regards safety laboratory tests, urinalysis, and vital signs measurements, presenting severe (grade 3) or greater results, according to the FDA toxicity grading scale, as well as clinically significant results, as assessed by the investigators, and evaluation of changes since baseline, as applicable, using descriptive statistics. More details will be included in the SAP.

7.11 Analysis of immunogenicity (exploratory endpoints)

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

7.12 Interim analysis

An early analysis of data available up to, and including, Visit 8 will be performed based on unblinded cleaned data. The analysis 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.

The early analysis will be conducted by an unblinded team within the CRO and the 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 site personal and study participants will remain blinded until the end of the study.

7.13 Sample size determinations

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 seroprotection levels (%) obtained, as defined by cut-points 0.5, 1.0, 2.0 and 4.0, are shown in the following table.

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 seroprotection levels corresponding to cut-point = 1 µg/ml as basis, the power of the non-inferiority tests described in Section 7.8, should be above 90 % if equal responses in the vaccination groups 1, 2 and 3 are assumed. For higher cut-points (2/4/8) this power will however most likely be smaller, in particular for the IgG corresponding to the Rib-N protein.

8 Ethical, legal and GCP aspects

8.1 Declaration of Helsinki and good clinical practice

The clinical study MVX0004 is planned, conducted and reported in compliance with this protocol, the latest version of the 'Declaration of Helsinki', the 'ICH E6 (R2)' and 'Directive 2001/20/EC' (to be replaced by 'EU Regulation 536/2014', when implemented).

8.2 Informed consent

The written subject information and the informed consent form will not be used until approved by the applicable IEC(s) and CA(s). All participants must provide written informed consent.

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

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

If the participant is willing to participate in the study, the ICF will be signed and personally dated by the participant and the person taking consent.

The participant will receive a copy of the ICF together with the participant information sheet and the original signed ICF will be retained with the study records at the investigational site. In addition, the actions and completion of the consenting process will be recorded in the participant's medical record (*i.e.*, source document).

Parental informed consent on behalf of fetus the baby to be born will be given according to national regulations applicable to the sites.

8.3 Independent Ethics committee submission and approval

The study will not be initiated until it has been approved by the applicable IEC(s).

The sponsor, or delegated CRO will, according to applicable guidelines and legislation and in collaboration with the site PIs, prepare a clinical trial application (CTA) to be submitted to the IECs, responsible for the respective investigational sites.

The expected timelines for approval are as given in the current guidelines/regulations ('Directive 2001/20/EC' to be replaced by 'EU Regulation 536/2014', when implemented) for Denmark, and for the UK, as given in current UK national guidelines/legislation applicable to IECs, and for South Africa as given in current local national legislation applicable to IECs.

8.4 Competent authority submission and approval

The study will not be initiated until it has been approved by the applicable CA(s).

The sponsor, or delegated CRO, will prepare a clinical trial application (CTA) to be submitted to the CAs in Denmark, the UK and in South Africa.

8.5 Personal data protection and confidentiality

MinevaX' processing of personal data is subject to regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC, General Data Protection Regulation (GDPR), Article 6(1)(c) and 9(2)(i), as well as various special legislation and guidelines related to the processing of health information in connection with clinical trials and registration of medicines.

The principal investigator is responsible for keeping a subject identification log of study subjects including personal identity information, e.g., full name, address, personal identification number etc.

The study documents containing personal identity information, e.g., the screening log and the signed informed consent forms, will be kept in a secure place, at the investigational site at all times, and will not be transferred to the sponsor or any third party at any time.

All other study documents, electronic records or labels on biological samples will not contain personal identity information but will identify the study subjects by use of a subject number and is this way pseudonymised (encrypted). Only, through linking the subject number to the screening log (kept in a secure place at the investigational site) the subject can be identified.

MinervaX may transfer or provide access to the personal data to entities located in countries outside the EU/EEA that the European Commission has not found to ensure an adequate level of protection of personal data. MinervaX will strive to ensure that adequate safeguards (contractual or otherwise) are in place (e.g, European Commission standard personal data protection clauses) to protect the privacy of personal data, however, this may not always be possible.

8.6 Investigator's responsibility and delegation of tasks

The site PI is responsible for the conduct of the clinical study in accordance with the protocol, ICH GCP E6 (R2), applicable standard operation procedures (SOPs), and applicable national law and regulations.

The site PI is responsible for supervising any individual or party to whom the investigator delegates study related tasks.

The site PI's delegation of study related tasks to appropriately qualified staff members must be documented in a signature and delegation log that is signed off by the staff members and the site PI, and by dated and signed curriculum vitae (C.V.s), for staff members with important tasks, such as investigators and site study coordinators.

The current signature and delegation log and the C.V.s must be kept in the investigator's site file (ISF).

Before the initiation of the study, the sponsor will collect copies of the completed signature and delegation log and the dated and signed C.V.s.

At the end of the study the signature and delegation log will be signed off for completeness by the site PI.

8.7 Indemnity statement

In the event that any recruited subject in the study should suffer any personal injury resulting from the clinical study, MinervaX agrees to indemnify the institution where the clinical study is being undertaken, and through the institution, any of its employees or agents participating in the study, against liability imposed by law, but not assumed voluntarily, and arising from the use of the investigational products, PROVIDED THAT:

1) MinervaX shall not indemnify against, nor have any obligation whatsoever as regards liability arising from or related to any error, omission, intentional wrongful act, or other negligence on the part of said institutions or persons, such as medical malpractice; and

2) Any such institution or person seeking indemnity

   a) has fully complied with the protocol for the study, and

   b) has promptly notified MinervaX of any notice of any type of claim, or the likelihood of a claim, relating to the study,

   c) as regards any claim, makes no statement, takes no action, nor makes any commitment affecting MinervaX's interests, without MinervaX's prior written consent, and further, provides all reasonable and necessary assistance to MinervaX in the defence of any claim, allowing MinervaX, at its cost and in its discretion to take over the defence of any action and to have full control in handling the claim.

8.8 Study oversight, quality management and monitoring

The sponsor, MinervaX, will implement a system to manage quality throughout all phases of the study, employing a risk-based approach, with a focus on aspects that are essential to ensure human subject protection and reliability of study results, and this way, ensuring adequate study oversight and monitoring at all times.

Clinical site monitoring is conducted to ensure that the human rights, well-being and safety of the study subjects are protected, that the reported study data are accurate, complete and verifiable, and that the conduct of the study is in compliance with the current protocol, applicable current SOPs, ICH GCP E6 (R2), and applicable national law and regulations.

During the course of the study, the blinded and unblinded monitors will visit the study site to ensure that the protocol and ICH GCP E6 (R2) are adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The monitoring visit intervals will depend on the study site's recruitment rate, the compliance of the study site with the protocol and ICH GCP E6 (R2).

Details of clinical site monitoring are documented in a monitoring manual. The manual describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed and the distribution of monitoring reports.

8.9 Audit and inspection

The investigational sites must give access to the sponsor's quality assurance (QA) staff for the conduct of audits and to inspectors from the CA or other relevant authority for the conduct of inspections.

Auditors and inspectors must have access to all study-related documents, including the subject screening log(s) and/or personal medical records.

The principal investigator will inform the sponsor immediately and vice versa, if an inspection has been requested by an authority.

8.10 Source documentation

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

At the investigational site, a document, which identifies all (expected) source documents and the location of these, will be prepared (and signed off by the site PIs) before the initiation of the study.

8.11 Archiving

It is the responsibility of the site PIs to retain all source data (all source documents from which the eCRF entries are derived) in the study subject's medical records for at least 25 years after the LSLV.

Essential documents are those documents which individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigators, sponsor and monitor with the standards of GCP.

Before initiation of the study an investigator's site file (ISF) will be set up at the investigational site and a trial master file (TMF) at the sponsor's site following the ICH GCP E6 (R2) guideline. These systems will contain the essential documents.

9 Agreement and financial settlement

Agreements including financial settlement between the principal investigator or the investigator institution and the sponsor or the sponsor's CRO, as applicable, will be signed off by the legal representatives of the parties prior to inclusion of the first subject in the study.

These agreements will clearly state the rights and obligations of the concerned parties and are the legally binding agreement between the parties. This protocol, in its present version, or in its current version at any time, in case of subsequent modifications (amendments), will be an appendix to the agreements between the principal investigator and the sponsor.

10 Liability and insurance

MinervaX is the sponsor of the study and responsible manufacturer of the investigational products to be administered in the study. MinervaX carries a product liability insurance programme including cover for clinical studies. The insurance programme covers worldwide and is currently placed with insurer Lloyd's Insurance Company S.A., through insurance brokers hertz & Ørum Forsikringsmæglere A/S, Denmark. The policy covers claims arising from injury/injuries caused by the study vaccines used in this clinical study sponsored by MinervaX, if the study vaccines were used in accordance with the instructions given in the protocol. Please see Section 8.7.

An updated insurance certificate will be provided separately, without updating the protocol, if applicable.

11 Confidentiality and disclosure

All eCRF data, information and results, as well as information on product development, patented or not, including patent applications and manufacturing processes not previously published, are considered confidential and shall remain the sole property of MinervaX.

No data from the clinical study, unless approved by MinervaX in writing, may be published, presented or communicated, except to CA(s) or EC(s), prior to being published.

12 Modifications to the protocol

The study procedures may be modified if the signing parties agree to the modifications.

If the modifications are substantial, the CA and IECs must be notified and approve the modifications prior to implementation. All substantial modifications should be documented by issuing new amended versions of the protocol implementing the modifications.

In case of administrative changes, such as changes in contact details, study staff (apart from the principal investigator), timelines or a new insurance certificate, a protocol amendment is not required.

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