Protocol MVX0002

A Phase I, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of two doses of Group B Streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in healthy female subjects aged 18 to 40.

Version:	4.0 (incorporating protocol amendments 1 and 2)
Version Date:	02 January 2019
EUDRACT Number:	2017-003871-27
Sponsor:	MinervaX ApS Ole Maaløes Vej 3 DK-2200 Copenhagen N Denmark
Phase:	Phase I
GCP Statement:	This study is to be performed in full compliance with ICH and all applicable local Good Clinical Practices and regulations.
Confidentiality:	This document is confidential. It contains proprietary information of MinervaX. Any viewing or disclosure of such information that is not authorised in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Table of Contents

1. APPROVAL SIGNATURES

[redacted]	Signature	Date
Principal Investigator		

1. APPROVAL SIGNATURES

[redacted] Medical Monitor	Signature	Date

- APPROVAL SIGNATURES

 MinervaX	Signature	Date

- **APPROVAL SIGNATURES**

[redacted] Biostatistician	Signature	Date

2. PROTOCOL REVISION HISTORY

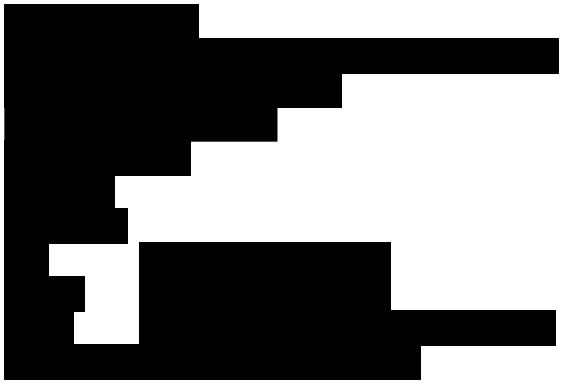
Date	Description
18 July 2017	Original Draft 0.1
30 Aug 2017	Draft 0.2
18 Sep 2017	Draft 0.3
26 Sep 2017	Draft 0.4
03 Oct 2017	Draft 0.5
17 Oct 2017	Draft 0.6
23 Oct 2017	Draft 0.7
13 Feb 2018	Draft 0.8
16 Feb 2018	Final 1.0
14 March 2018	Version 2.0 Sections 9.1, 10, 12.7, modified in response to GNA letter
12 December 2018	Administrative changes to Sections 3, 12.1, 12.2, 13.1, 15.4 and 18 Change in PD laboratory and correction of inconsistencies. Transcription error in the EUDRACT number corrected.
02 January 2019	Total blood volume draw corrected, correction of typographical Error Section 13

3. STUDY CONTACTS

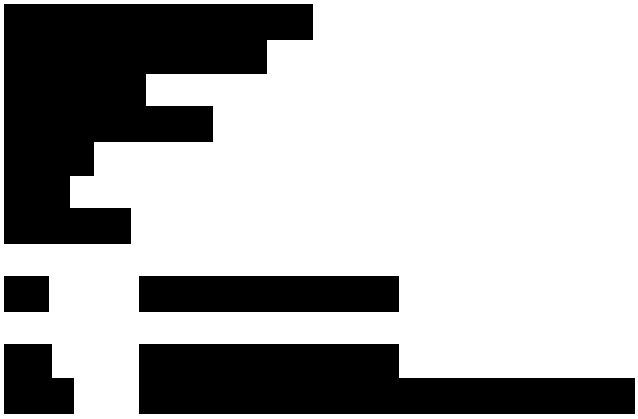
PRINCIPAL INVESTIGATOR

INVESTIGATIONAL SITE

24 HOUR SPONSOR MEDICAL MONITOR



SAFETY REPORTING



SAFETY LABORATORIES

[redacted]

STATISTICS

[redacted]

ANALYSIS OF PHARMACODYNAMIC BLOOD SAMPLES

[redacted]

And

[redacted]

4. SYNOPSIS

Protocol Number:	MVX0002
CRO Protocol Number:	RD 751/33819
Study Vaccine(s):	Group B Streptococcus Vaccine(GBS-NN/NN2)
Title:	A Phase I, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of two doses of Group B Streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in healthy female subjects aged 18 to 40.
EudraCT Number:	2017-003871
Objectives and Endpoints:	**Primary Objective** • The primary objective is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine for 12 weeks (up to Day 85) after the first dose of vaccine. • **Secondary Objectives** • To evaluate IgG antibody responses induced by the two vaccine doses of GBS-NN/NN2 up to Day 85 in healthy female subjects. • To assess whether pre-existing antibody levels affect the vaccine-induced antibody response. • **Exploratory Objectives** • [redacted] • **Primary Endpoints** • Local and systemic reactogenicity; adverse events; laboratory tests; urinalysis; vital signs; physical examination. • **Secondary Endpoints** • Local and systemic reactogenicity; adverse events; laboratory tests if undertaken for cause; urinalysis if undertaken for cause; vital signs; physical examination the outcome of any pregnancies. • Geometric mean antibody concentration in µg/mL.

<table>
<tr><td></td><td>

Geometric mean fold increase in antibody concentration.
Seroconversion rate (proportion of subjects with fold increase above threshold at any time post vaccination).
Proportion of subjects achieving antibody concentrations above specific thresholds at Days 29 & 85 (these will be 2, 4, 8 μg/mL). This will provide an assessment of the immune response to the first and second doses.

</td></tr>
<tr><td>Study Design:</td><td>This is a Phase I, randomised, double-blind, placebo-controlled, parallel group, single centre study.

There will be 2 cohorts of 30 subjects. Cohort 1 will receive two 0.5 mL injections, 4 weeks apart, each consisting of 25 μg of GBS-NN and 25 μg of GBS-NN2 (24 subjects) or placebo (6 subjects). Cohort 2 (30 subjects) will receive two 0.5 mL injections, 4 weeks apart, each consisting of 50 μg of GBS-NN and 50 μg of GBS-NN2 (24 subjects) or placebo (6 Subjects). All vaccines will be adsorbed to 500 μg Al3+ as Alhydrogel®.

Safety will be assessed after all subjects have completed Visit 4 (Day 8) for Cohort 1, at which point the decision will be made as to whether proceeding with administration of the doses in cohort 2 is appropriate.</td></tr>
<tr><td>Study Duration:</td><td>Study start is defined as check-in to the study unit on Day 1. Each individual subject will be involved in the study for approximately 12 weeks (excluding the 28 day screening period and the 6 month safety follow up).</td></tr>
<tr><td>Study Population:</td><td>60 healthy female subjects aged 18 to 40 will be randomised into 2 cohorts of 30 subjects.</td></tr>
<tr><td>Investigational Medicinal Product and mode of administration</td><td>GBS-NN/NN2 vaccine will be supplied [redacted]

The placebo vaccine will contain Alhydrogel® mixed with sterile dilution buffer.</td></tr>
<tr><td>Selection of Dose</td><td>The GBS-NN/NN2 vaccine will be supplied a [redacted]

The placebo vaccine will contain Alhydrogel® mixed with sterile dilution buffer.

[redacted]

Individual subject treatments will be dispensed by the pharmacist or designee and labelled in accordance with Annex 13 of “The Rules Governing Medical Products in European Community, volume 4 Good Manufacturing Practice for Medicinal Products”.

The following dosing strategy will be employed:
<table>
<tr><th>Cohort</th><th>Dose schedule</th><th>Dose level GBS-NN/NN2 or placebo</th></tr>
<tr><td>1</td><td>Day 1, 29</td><td>25μg of each protein or placebo</td></tr>
<tr><td>2</td><td>Day 1, 29</td><td>50μg of each protein or placebo</td></tr>
</table>
</td></tr>
<tr><td>Treatment Schedule</td><td>Volunteers will provide written informed consent and will be screened for eligibility within 28 days before first study vaccine administration (Day 1). Study start is defined as check-in to the study unit on Day 1. Each individual subject will be involved in the study for approximately 12 weeks (excluding</td></tr>
</table>

	the 28-day screening period and the 6-month safety follow up). Eligible Subjects will be administered the primary dose of the appropriate dose of GBS-NN/NN2 or placebo according to the cohort and dosing schedule described in section 10.1. at Visit 2 and a second dose will be administered at Visit 6. All cohorts will incorporate sentinel dosing of 2 subjects in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further subjects in that cohort will be dosed until 24 hours after dosing the second subject, provided that there are no serious or unexplained safety issues as determined by the Investigator. The decision to proceed with administration of the primary dose in the subsequent cohort will be made as described in Section 12.5. A safety follow-up visit will be performed 6 months (±2 weeks) following the second study vaccine administration to check the general health collect blood for haematology, biochemistry and to assess the immune response. of the subject and to review adverse events (AEs).
Statistical Analysis:	Statistical analyses will be performed by [redacted] using SAS 9.3 or higher. Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), minimum, median and maximum. Descriptive statistics for qualitative parameters will be provided using absolute frequencies (n) and relative frequencies (%). For immunological endpoints (IgG concentration and fold increase) additionally geometric means with corresponding 95% confidence intervals will be presented. Demographic, baseline characteristics and data recorded during the study will be summarized using descriptive statistics by treatment (placebo or vaccine) and dose group, unless otherwise specified. Individual data will be presented as a data listing, sorted by treatment and administered dose level. For parameters with evaluation before vaccination and in case of re-checked value(s), only the last observation prior to dosing will be used in descriptive and inferential statistics and derivations of other parameter values. After vaccination, only values of scheduled assessments (planned in the protocol) will be used. Statistical tests will be carried out to compare results between treatment groups, depending on studied variable type. These analyses will be fully detailed in the SAP. For categorical endpoints, such as local and systemic reactogenicity, a comparison of events intensity (scores) between vaccine dose groups can be performed with an adequate statistical test dealing with categorical variables (for example: Fisher exact test, Chi square test or generalized estimating equations). For continuous endpoints, such as immune response induced by different GBS-NN/NN2 vaccine dosing regimens, appropriate statistical method (for example: ANOVA or ANCOVA) can be used to compare pre-vaccination and post-vaccination levels as well as post-vaccination levels between groups.

5. LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic and Therapeutic Class
AUC	Area Under the Curve
BMI	Body Mass Index
CA	Competent Authority
CPS	Capsule Polysaccharide
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically Significant
EC	Ethics Committee
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
EOD	Early Onset Disease
EU	European Union
FACS	Fluorescence-Activated Cell Sorting
FSH	Follicle Stimulating Hormone
GBS	Group B Streptococcus
GBS-NN	Group B Streptococcus vaccine component no 1
GBS-NN2	Group B Streptococcus vaccine component no 2
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMT	Geometric Mean Titre
HIV	Human Immunodeficiency Virus
IAP	Inter Partum Antibiotic Prophylaxis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IG	Immunogenicity Set
IS	Included Set
IUD	Intra Uterine Device
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LOD	Late Onset Disease

MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NTEAE	Non Treatment Emergent Adverse Event
OPA	Opsonophagocytic Killing Assay
PBMC	Peripheral Blood Mononuclear Cell
PP	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SEM	Standard Error of the Mean
SMB	Safety Monitoring Board
SOC	System Organ Class
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
Th cells	T helper cells
TOPS	The Over Subjecting Prevention System
VIS	Subject Information Sheet

6. INTRODUCTION

6.1 Background

Group B Streptococcus (GBS) has now emerged as the leading cause of neonatal sepsis and is also increasingly recognised as an important cause of disease in adults, especially in the elderly and those with underlying disease (Schrag et al., 2000, Skoff et al., 2009). In fact, GBS is responsible for 50% of life-threatening infections in newborns, leading to severe morbidity and life-long disabilities. In particular, GBS is responsible for over 80% of meningitis in neonates less than 2 months of age (CDC, 2010 Vol.59).

GBS neonatal infections are associated with high morbidity and mortality and constitute a major public health problem affecting 0.5 to 3 new-borns per 1000 live births (CDC 2002). In the UK, national surveillance during 2000-2001 identified a total of 568 cases; an incidence of 0.72 per 1000 live births, showing regional variation with 0.42 per 1000 live births in Scotland and 0.9 in Northern Ireland. GBS neonatal infections have been reported in and across Europe, USA, Australasia, South Africa, Kenya and Malawi confirming the global nature of the disease.

GBS related neonatal morbidity can be classified into Early Onset Disease (EOD; occurring 1 to 6 days after birth), and Late Onset Disease (LOD; occurring 7 to 89 days after birth). EOD accounts for about 60 to 70% of GBS related neonatal morbidity as a result of vertical transmission of GBS from mother to infant at or around the time of delivery. In over 90% of cases, clinical features of sepsis and pneumonia occur within 12 to 24 hours (Heath et al., 2004, 2009). In contrast LOD, which occurs 7 to 89 days post-delivery, and is acquired perinatally, nosocomially or from community sources, presenting with meningitis in up to 50% of cases (Heath et al., 2004). There is also an association with GBS urinary tract infection and the occurrence of chorioamnionitis, and premature labour (Anderson et al., 2007; Thomsen et al., 1987).

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

Despite this widespread use of IAP, EOD has not been reduced by more than 80% at the most, and still affects some 4,500 new-born babies annually in Europe and the US combined; and the incidences have recently been on the rise again (Health Protection Agency UK, 2012 Vol.6). The failure of IAP to fully eradicate EOD relates primarily to lack of adherence to protocol, poor implementation of protocols, premature delivery, and childbirth lasting less than the 4 hours required for IAP to be fully active.

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

In addition to the inability of IAP to completely eradicate EOD and in anyway prevent GBS-induced LOD, stillbirth and preterm labour, the widespread use of antibiotic prophylaxis in GBS prevention has resulted in the emergence of antibiotic resistance in GBS. Penicillin remains the preferred antibiotic prophylaxis, but clinical isolates with reduced sensitivity to penicillin due to mutations in penicillin-binding proteins have emerged over recent years (CDC, 2010 Vol.59)

(Kimura, 2008 Vol.52). The alarming finding is that the emerging patterns of mutations are identical to those observed in *S. pneumoniae* prior to the breakthrough of widespread true penicillin resistance in that pathogen (Dahesh, 2008 Vol. 52) (Nagano, 2008 Vol.52). Full breakthrough of penicillin resistance in GBS will lead to a dramatic increase in the incidences of EOD, potentially returning the world to pre-IAP levels, as well as creating a serious problem when having to treat such infections. In addition, wide-spread resistance to antibiotics other than penicillin already exists in GBS isolates (CDC, 2010 Vol.59). Finally, IAP has also led to an increase in neonatal infections with antibiotic resistant strains of other bacteria such as *E.coli*.

6.2 Rationale for Study

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

Immunization of pregnant women during the latter part of pregnancy leading to passive immunization of the unborn child through trans-placental transfer of protective GBS-specific antibodies would be beneficial. Such antibodies will likely persist for 3-6 months after birth and potentially protect the foetus in-utero, against GBS induced still birth and premature delivery; and the newborn baby against both EOD and LOD. A vaccine therefore seems the obvious choice for an alternative to IAP (Madhi et al 2016, Donders et al 2016, Heyderman et al 2016).

A number of GBS serotypes can be distinguished based on their type-specific capsular polysaccharides (CPS). This capsule represents a major virulence factor, which helps bacterial invasion by interfering with phagocytic clearance except in the presence of type specific opsonophagocytic antibodies (Baker 2000, Nizer et al., 2000). To date, 10 antigenically unique GBS serotypes have been identified (Ia, Ib, II-IX). Of these serotypes Ia, III and V are the most prevalent in EOD with type III accounting for 36% of EOD and 71 % of LOD, and together, serotypes Ia, Ib, II, III and V cover approximately 95% of all isolates.

Spontaneous colonization of women with GBS is the likely explanation for the existence of naturally occurring antibodies against several GBS antigens in pregnant women. Interestingly, the presence of high levels of anti-CPS antibodies in pregnant women has been found to correlate with protection of their off-spring against invasive GBS disease, indicating that vaccine-induced maternal anti-CPS antibodies would indeed be protective (Baker and Kasper, 1976; Lin et al., 2001; Lin et al., 2004).

MinervaX has developed a novel GBS vaccine candidate, GBS-NN, based on the N-terminals of the Rib and AlphaC surface proteins of GBS. Rib and AlphaC, and cross-reactive Alpha-like proteins (Alp 1 and Alp2/3; Alp2 and Alp3 have an identical N-terminal domains) that are found on most isolates of serotypes Ia, Ib, II, III, IV, V, VI, VII and VIII, and antibodies directed against the vaccine were found to recognize 80-100% of 154 clinical isolates of serotypes Ia, Ib, II, III and V tested for antibody binding. Naturally occurring antibodies against the full-length Rib and AlphaC proteins are found in pregnant women, likely due to exposure to GBS from colonization, and such antibodies are efficiently transferred to their babies in-utero. Antibodies to Rib and AlphaC elicit protective immunity in animal models when administered with the standard adjuvant alum (Larsson et al., 1999).

The first clinical trial with GBS-NN, in healthy non-pregnant women, has shown the potential vaccine to be highly immunogenic well tolerated with a good safety profile. Investigations into the breadth of coverage of the GBS-NN vaccine against all GBS strains have identified the need for the additional antigens, Alp1, Alp2, and Alp3 to be included in a vaccine. GBS-NN2 contains the Alp1, Alp2 and Alp3 N-terminal proteins (Alp2 N and Alp3 N are identical) and has been added to GBS-NN. Hence, of the four different members of the targeted surface proteins that are found on different GBS bacteria, two are represented in GBS-NN and the remaining two in GBS-NN2. MinervaX has completed toxicology studies on the GBS-NN/NN2 vaccine, which is

now ready to move into clinical trials, in a population of healthy, non-pregnant female subjects.

6.2.1 Summary of Non Clinical Data

Mice have been dosed with GBS-NN with and without alum at doses ranging from 2µg to 64µg [redacted] immune responses were elicited at all doses, with the antibody responses at doses of 4µg to 64µg in the presence of Alhydrogel® being indistinguishable from each other and showing a trend towards being higher than responses to 2 µg [redacted]. The addition of alum reduced the time taken for the peak immune response to be achieved, increased the magnitude of the immune response and increased the number of responders.

The local and systemic toxicity studies with GBS-NN/NN2 in rabbits and rats, respectively, did not identify any unexpected findings. [redacted]r.

The findings of the studies are in line with the findings GBS-NN alone and the changes seen in the animals were considered to be the pharmacological responses to the vaccine inducing an immune response. [redacted]

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

Reproductive toxicology studies are being completed, preliminary data has not identified any adverse effect on foetuses or foetal development.

Immunogenicity studies with GBS-NN/NN2 have been undertaken in mice [redacted]. Immunisation with either GBS-NN or GBS-NN2 induces significant cross-reactivity with the heterologous antigen. Primary immunization with the combination of GBS-NN and GBS-NN2 gives similar responses to all four domains and the responses to homologous antigens are equivalent to those induced by immunizing with the single molecules.

6.2.2 Summary of Clinical Data

Study MVX13211 with GBS-NN alone, has shown that GBS-NN is well tolerated in healthy female subjects. The study concluded that GBS-NN has an appropriate safety profile for a vaccine with the primary adverse reaction of pain at injection site was mild and reported at an incidence comparable to other intramuscularly administered vaccines that contain Alhydrogel®. Healthy subjects developed high concentrations of antibodies against the N-terminal proteins AlphaC and Rib [redacted], if the antibodies are protective, it is anticipated that the foetus will be passively immunized from the mother.

The first clinical trial with GBS-NN, in healthy non-pregnant women, has shown the potential

vaccine to be highly immunogenic when 2 doses of 50 µg or one or two doses of 100 µg were administered with Alhydrogel®. [redacted] These studies have identified the need for the additional antigens, Alp1, Alp2 and Alp3 to be included in a vaccine. GBS-NN2 contains the Alp1, Alp2 and Alp3 N-terminal proteins (Alp2 N and Alp3 N are identical) and has been added to GBS-NN, in order to confer protection against all clinical isolates of GBS. Hence, of the four different members of the targeted surface proteins that are found on different GBS bacteria, two are represented in GBS-NN and the remaining two in GBS-NN2. [redacted]

GBS-NN demonstrated a good safety profile with most adverse events (AEs) being mild and related to injection site reactions, no serious adverse events related to GBS-NN were reported. It is anticipated that the GBS-NN/NN2 vaccine will have a similar profile, as the two additional N-terminal proteins are very similar in structure to the original GBS-NN proteins. Animal toxicology studies showed similar toxicity profiles for GBS-NN and GBS-NN/NN2.

Cross reactivity with the other N-terminal proteins Alp1, Alp2 and Alp3 was not of the anticipated magnitude and the addition of these proteins is considered necessary to broaden the coverage of the vaccine against pathogenic strains of GBS. Hence, the GBS-NN vaccine will be investigated in a study of a similar design to Part B of MVX13211, as the initial study before moving to investigate safety in pregnant women.

6.3 Risk/Benefit Assessment

Antibodies against the full-length Rib, AlphaC, Alp1, Alp2 and Alp3 proteins, from which the GBS-NN and GBS-NN2 are derived to make up the vaccine antigens, naturally occur in women exposed to GBS, and such antibodies are efficiently transferred to the unborn child *in-utero.* Many adults and new-born infants have, therefore, already been naturally exposed to the proteins from which the antigen is derived and to antibodies against these proteins, and no side effects have been attributed as a consequence of such exposure in humans.

[redacted]. The maximum human dose will be 50 µg, which if administered to a 60 kg woman would equate to 0.83 µg/kg giving a safety margin of at least 60-fold.

The planned excipients in the vaccine formulation are also all well-known from other vaccines, and no novel or non-tested components are used. The proteins in the vaccine are adsorbed with a known adjuvant, Alhydrogel®, (0.5 mg of Al^{3+} per dose), corresponding to the dose used in many other commercial vaccines.

[redacted]

This is a new investigational product; therefore, there are currently no expected AEs related to the product. However, following injection of GBS-NN alone, approximately 30% of the subjects in the study experienced mild pain. Pain post-injection that is worse that mild would be considered to be unexpected. It is not anticipated that adding the two additional antigenic proteins, to GBS-NN, bound to Alum will significantly alter the safety profile. The Investigator is responsible for reporting adverse events (AEs) that occur during the course of the study. Serious adverse reactions that are deemed to be related to the investigational product in the proposed study will be reported as suspected unexpected serious adverse events (SUSAR).

GBS-NN/NN2, like other protein-based vaccines, may theoretically be associated with a transient febrile reaction (body temperature greater than 38.0°C but not greater than 38.7°C) following vaccination. Immune complex-mediated reactions are unlikely given the recombinant nature of GBS-NN/NN2, however, it is still possible that hypersensitivity may occur.

Based on the results from clinical use of other protein vaccines adsorbed to Alhydrogel®, and other aluminium containing adjuvants transient local reactions at the injection site, including pain, oedema, bruising, erythema and induration, mainly of mild intensity, are likely to occur. In addition, flu-like symptoms, such as fatigue, malaise, myalgia, and mild to moderate headache may occur.

The protocol requires that subjects are monitored after vaccine administration (vital signs and general signs and symptoms), with regular follow-up visits for physician assessment and questioning regarding AEs will be conducted for all subjects in the study. All study subjects will be monitored for potential side effects of vaccination during the entire course of the study, as per the protocol, and adverse events must be appropriately followed up.

GBS-NN/NN2 vaccination is contraindicated in subjects known to suffer hypersensitivity reactions to vaccines or a known allergy to aluminium hydroxide. For the purpose of the study subjects who have experienced a significant illness in the four weeks prior to check in will be excluded. The vaccine should not be given to subjects with known or suspected immune deficiency, autoimmune diseases or who have an acute infection.

GBS-NN/NN2 should not currently be given to women known, or suspected to be, pregnant, or to nursing mothers. Currently GBS-NN/NN2 should only be administered to women of child-bearing potential if adequate contraceptive precautions are taken, accompanied by serum and/or urine pregnancy testing prior to vaccination and during follow up.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

- The primary objective is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine for 12 weeks (up to Day 85) after the first dose of vaccine.

7.2 Secondary Objectives

- To evaluate IgG antibody responses induced by the two vaccine doses of GBS-NN/NN2 up to Day 85 in healthy female subjects.
- To assess whether pre-existing antibody levels affect the vaccine-induced antibody response.

7.3 [redacted]

[redacted] pregnancy.

7.4 Primary Endpoints

- Local and systemic reactogenicity; adverse events; laboratory tests; urinalysis; vital signs; physical examination.

7.5 Secondary Endpoints

- Local and systemic reactogenicity; adverse events; laboratory tests if undertaken for cause; urinalysis if undertaken for cause; vital signs; physical examination; the outcome of any pregnancies.
- Geometric mean antibody concentration in μg/mL.
- Geometric mean fold increase in antibody concentration.
- Seroconversion rate (proportion of subjects with fold increase above threshold at any time post vaccination).
- Proportion of subjects achieving antibody concentrations above specific thresholds at Days 29 & 85 (these will be 2, 4, 8 μg/mL). This will provide an assessment of the immune response to the first and second doses.

8. STUDY DESIGN

8.1 Overview

This is a Phase I, randomised, double-blind, placebo-controlled, parallel group, single centre study.

There will be 2 cohorts of 30 subjects. Cohort 1 will receive two 0.5 mL injections, 4 weeks apart, each consisting of 25 μg of GBS-NN and 25 μg of GBS-NN2 (24 subjects) or placebo (6 subjects). Cohort 2 (30 subjects) will receive two 0.5 mL injections, 4 weeks apart, each consisting of 50 μg of GBS-NN and 50 μg of GBS-NN2 (24 subjects) or placebo (6 Subjects). All vaccines will be adsorbed to 500 μg Al^{3+} as Alhydrogel®.

Safety will be assessed in a blinded fashion after all subjects have completed Visit 4 (Day 8) for Cohort 1 , at which point the decision will be made as to whether proceeding with administration of the doses in cohort 2 is appropriate.

8.2 Study Centre(s)

The study will be performed at a single centre based in the United Kingdom.

8.3 Study Duration

Study start is defined as check-in to the study unit on Day 1. Each individual subject will be involved in the study for approximately 12 weeks (excluding the 28 day screening period and the 6 month safety follow up).

9. STUDY POPULATION

9.1 Inclusion Criteria

1. Healthy female subjects aged 18 – 40 years.
2. Body mass index (BMI) ≥18 and ≤30 kg/m^2.
3. Subjects weight ≥50kg and ≤100kg at screening.
4. Able to voluntarily provide written informed consent to participate in the study.
5. Subjects are pre-menopausal.
6. Females of childbearing potential must have a negative pregnancy test at screening (β HCG) and prior to each dose. To prevent pregnancy female subjects of childbearing potential must take adequate contraceptive precautions for the entire duration of study participation (up to Day 85). Adequate and highly effective contraceptive precautions include:
    - Established use of oral, injected or implanted hormonal methods of contraception.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
    - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects, the vasectomised male partner should be the sole partner for that subject].
    - True abstinence, when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
    - The chosen contraception method(s) must be followed from the first dose until at least Day 85 of the study.
7. Non-smokers for at least 3 months prior to first study vaccine administration.

9.2 Exclusion Criteria

1. Subjects who have received GBS-NN vaccine previously.
2. Subjects with history or presence of significant cardiovascular disease, pulmonary, hepatic, gallbladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, autoimmune disease or current infection.
3. Pregnant or lactating females.
4. Laboratory values at screening which are deemed by the investigator to be clinically significantly abnormal.
5. Positive drug screen for drugs of abuse or a positive alcohol urine test prior to first dosing unless there is a documented medical explanation for the positive result other than drugs of abuse (e.g., the subject has been prescribed opioids for pain).
6. Positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
7. Participation in a clinical drug study during the 90 days preceding the initial dose in this study.

8. Any significant illness during the 4 weeks preceding check-in for this study (Day 1).
9. Subjects with a history of allergic reactions after previous vaccination.
10. Subjects who have received any vaccine within 30 days of screening, or who are planning to receive a vaccine up to Day 85 of the study.
11. Subjects receiving immunosuppressive therapy in the 6 months prior to screening, taking any short-term medications including over-the-counter (OTC) preparations, within 7 days of the first dose. Chronic medications such as antihypertensives, bronchodilators, oral contraceptives or statins that do not affect the immune system, will be permitted and allowed to continue during the study at the discretion of the Investigator. Paracetamol will be permitted for the treatment of headache or other symptoms. Use of OTC vitamins and dietary supplements is allowed
12. Subjects with tattoos at the proposed site of vaccine administration.
13. Donation of blood or blood products within 90 days prior to vaccine administration or intending to donate blood or blood products within 90 days of the last visit.
14. Subjects who, in the opinion of the Investigator, are unsuitable for participation in the study.

9.3 Planned Sample Size

60 healthy female subjects aged 18 to 40 will be randomised into 2 cohorts of 30 subjects.

At least 24 evaluable subjects in cohort 1 will be required to attend through to visit 4 in order to provide sufficient data for a decision to dose escalate in cohort 2. If the required number of evaluable subjects are not obtained in a cohort, then the safety review committee (SRC) must decide whether there is enough safety information available to make a decision or whether further subjects should replace the dropped subjects or if sufficient information exists to determine if the dosing of cohort 2 is appropriate.

9.4 Allocation of Randomisation Numbers

Subjects will be allocated to treatment groups according to a randomisation code produced by [redacted] using the PROC PLAN procedure of SAS® version 9.3.

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

9.5 Subject Withdrawal

The subject has the right to abstain from participation in the study or to withdraw consent to participate at any time. The Sponsor or the Investigator also holds the responsibility to withdraw a randomised subject from the study prematurely if it is considered in the best interest of the subject. The entire study may be stopped if there are unpredicted safety concerns.

A subject's participation may be discontinued at any point during the study without implications on further medical care if:

- They no longer wish to participate.
- The physician feels it is in their best interest to withdraw.
- The subject deviates from the treatment plan specified in the protocol (e.g. failure to attend essential or significant amount of study visits).

- The subject is no longer willing to comply with the requirements of the study protocol.
- The study is prematurely terminated, see Section 9.7.

If the participation of any subject ceases prematurely, the reasons leading to withdrawal from the study should be described in detail. A post-study medical should be performed as described in Section 12.2. The case report form (CRF) must be completed as fully as possible giving reasons for withdrawal when available. If a subject become pregnant between Day 1 (first dose) and Day 85, she will not receive any further vaccinations (if conception occurs between the first and second dose) but will undergo all follow-up visits and the pregnancy will be followed to term to determine the outcome unless the subject withdraws consent.

9.6 Subject Replacement

If the required number of evaluable subjects are not obtained in a cohort, then replacement subjects may be recruited as per section 9.3.

9.7 Premature Termination of the Study

Following review by the Sponsor and the Investigator, the study may be terminated prematurely if:

- There are new toxicological or pharmacological findings, serious adverse events (AEs) or frequent severe AEs likely to be related to the vaccine that invalidate the positive benefit-risk assessment.
- AEs occur in such prominence (i.e. severity and frequency) that the proposed schedule can no longer be adhered to.
- Significant protocol deviations occur at a frequency implicating the valid and safe conduct of the study.
- The Sponsor decides to discontinue the study.

The individual stopping criteria and study stopping criteria are described in Sections 12.6 and 12.7.

10. INVESTIGATIONAL MEDICINAL PRODUCT

10.1 Identity and Doses of IMP

The GBS-NN/NN2 vaccine will be supplied [redacted]

[redacted]

Individual subject treatments will be dispensed by the pharmacist or designee and labelled in accordance with Annex 13 of "The Rules Governing Medical Products in European Community, volume 4 Good Manufacturing Practice for Medicinal Products". Finished doses will be certified by the [redacted] Qualified Person.

The following dosing strategy will be employed:

Cohort	Dose schedule	Dose level GBS-NN/NN2 or placebo
1	Day 1, 29	25µg of each protein or placebo
2	Day 1, 29	50µg of each protein or placebo

10.2 Rationale for doses

[redacted] Hence, investigating the immune response of doses of 25 µg and 50 µg of each fusion protein was determined to be the most appropriate doses. There are no data to suggest that different amounts of each fusion protein are required and therefore equal amounts of each is considered appropriate.

10.3 Randomisation

Subjects will be randomised pre-dose on the morning of Day 1, once all eligibility criteria have been verified. A randomisation list will be held on site, which will be accessible only to unblinded study personnel.

10.4 IMP Administration

Administration will be by intramuscular injection into the deltoid muscle of one of the subject's arms. For the second dose the subjects opposite arm should be used in the event that the first injection site has not healed.

10.5 Blinding

This is a double-blind study. The study vaccine will be prepared at the study site by an unblinded pharmacy team as detailed in a separate pharmacy instruction manual. The Investigator will have access to emergency envelopes at all times. In case of an emergency or any finding that requires unblinding to determine the identification of the treatment

administered for the appropriate management of a subject on the study, the Investigator may break the blinding code for an individual subject. If the blind is broken the Investigator will inform the Sponsor within 24 hours of breaking the blind, that the blind has been broken and the reason for breaking the blind (but not necessarily the outcome of the breaking of the blind) and record the date/time and reason for breaking the blind.

10.6 Vaccine Accountability and Storage

The Investigator and study staff will be responsible for the accountability of all study vaccines (dispensing, inventory and record keeping) and adherence to Good Clinical Practice (GCP) guidelines as well as appropriate regulations. Study vaccines will be stored according to the instructions on the label as received by the manufacturer. Storage of GBS-NN and GBS-NN2 will be [redacted] Alhydrogel® and diluents buffer will be stored at 2 to 8°C.

The Investigator will not allow the study vaccine to be used other than as directed by this protocol. Study vaccines will not be dispensed to any individual who is not randomised in the study.

An accurate and timely record of the receipt of all study vaccines, dispensing to subjects, collection of unused study vaccines returned, and subsequent return of unused study vaccines to the Sponsor (or designated distributor) must be maintained. This includes, but may not be limited to, receipt of study vaccines, IMP accountability logs, IMP return documentation and shipping receipts.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of the Sponsor or a representative of a regulatory authority. All unused study vaccines will be reconciled and handled in agreement with the Sponsor.

The Investigator must ensure the availability of an appropriate storage location and the recording and evaluation of storage conditions. The Pharmacy Department will keep an inventory. This will include a description of the formulation and the quantity of investigational materials received for the study and a record of the materials that are dispensed, to whom and when.

Upon termination of the study the pharmacist or designee will conduct a final inventory of the medication supply and will record the results of this inventory in the Drug Accountability Form. Unused medication will be returned to the Sponsor (or designated distributor) or destroyed at the end of the study according to instructions provided by the Sponsor.

11. PRIOR AND CONCOMITANT MEDICATION, AND OTHER RESTRICTIONS

11.1 Prior Medications

Chronic medications such as antihypertensives, bronchodilators, oral contraceptives or statins that do not affect the immune system, will be permitted and allowed to continue during the study at the discretion of the Investigator.

Non-permitted medications are provided in the exclusion criteria Section 9.2.

11.2 Concomitant Medications

Paracetamol will be permitted for the treatment of headache or other symptomatic pains.

Any medication the subject takes, other than study vaccine and approved medications approved by the PI will be considered a concomitant medication; this will include herbal and other remedies. All concomitant medications taken during the study must be recorded in the CRF.

11.3 Other Restrictions

The Investigator or designee will request that subjects abstain from:

- Donation of blood or blood products for 90 days after the last dose of trial medication.
- Consumption of alcoholic beverages within 24 hours prior and post dosing and scheduled clinic visits.
- Use of cosmetics or creams at the site of vaccination that are known to cause irritation within 24 hours prior to dosing and for the duration of the study.
- Excessive exercise or a significant change in usual exercise habit within 7 days prior to dosing and for 7 days post dosing.

12. STUDY CONDUCT

Please refer to the schedule of assessments (Table 1, section 18) for a detailed overview of the study conduct.

12.1 Screening Period

Screening assessments will be performed within 28 days prior to the first study vaccine administration (Day 1). The following assessments will be carried out at the screening visit (Visit 1) after written informed consent has been obtained:

- Inclusion/Exclusion
- Demography
- Medical history
- Physical examination
- Height, weight, body mass index (BMI)
- Vital signs (heart rate, blood pressure, oral temperature and respiration rate)
- 12-lead electrocardiogram (ECG)
- Urinalysis
- Blood samples for haematology and biochemistry
- Blood samples for HIV, hepatitis B and hepatitis C
- Serum pregnancy test for females of child-bearing potential
- Alcohol urine test
- Urine drugs of abuse test Cannabinoids, amphetamines, cocaine, benzodiazepines, opiates and cotinine.
- A review of all medications taken in the previous month

12.2 Treatment Period and Post-Study Period

Subjects will be administered the primary dose of the appropriate dose of GBS-NN/NN2 or placebo according to the cohort and dosing schedule described in section 10.1 at Visit 2 and a second dose will be administered at Visit 6.All cohorts will incorporate sentinel dosing of 2 subjects in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further subjects in that cohort will be dosed until 24 hours after dosing the second subject, provided that there are no serious or unexplained safety issues as determined by the Investigator.

The decision to proceed with administration of the primary dose in the subsequent cohort will be made as described in Section 12.5.

The following assessments will be carried out at these visits:

Visit 2

A general medical review, vital signs, urine pregnancy test, urine drugs of abuse test and alcohol urine test will be performed to re-confirm eligibility. Eligible subjects will then be randomised to receive the appropriate treatment as per the randomisation list for the cohort. A pharmacodynamic blood sample will be taken to measure pre-existing antibody levels and to obtain Peripheral Blood Mononuclear Cells (PBMCs) to assess cellular responses, prior to

dosing. Blood sample for haematology and serum biochemistry will be taken. Vital signs will be recorded at pre-dose (within 60 minutes of dosing), 2 (±0.25) and 4 (±0.25) hours post-dose. A general medical examination (including an assessment of the injection site) will be performed prior to discharge to ensure the subject is fit for discharge. At discharge subjects will be provided with oral temperature kit and instructed to record a temperature if they feel unwell in the seven days post dose.

Visit 3

Visit 3 will be performed 24 hours (±2 hours) after administration of the primary dose and an assessment of the injection site will be performed, vital signs will be recorded and AEs and concomitant medications will be reviewed.

Visit 4

Visit 4 will be performed 1 week (±1 day) after administration of the primary dose. An assessment of the injection site will be performed, vital signs will be recorded, safety blood samples for haematology and biochemistry will be collected, urinalysis will be performed and AEs and concomitant medications will be reviewed.

Visit 5

Visit 5 will be performed 2 weeks (±2 days) after administration of the primary dose. This visit will review of AEs and concomitant medications. An assessment of the injection site will be performed, vital signs will be recorded, safety blood samples for haematology and biochemistry will be collected and a pharmacodynamic blood sample will be taken to measure the antibody response.

Visit 6

Visit 6 will be performed 4 weeks (±3 days) after Visit 2. An assessment of the injection site, AEs and concomitant medications review, urine pregnancy test, and a pharmacodynamic blood sample will be taken to measure the antibody response prior to administering the second dose. Vital signs will be recorded pre-dose and at 2 (±0.25) and 4 (±0.25) hours post-dose. A brief medical examination (including an assessment of the injection sites) will be performed prior to discharge to ensure the subject is fit for discharge. At discharge subjects will be provided with oral temperature kit and instructed to record a temperature if they feel unwell in the 7 days post dose.

Visit 7

Visit 7 will be performed 24 hours (±2 hours) after administration of the booster dose and an assessment of the injection sites will be performed, vital signs will be recorded and AEs and concomitant medications will be reviewed.

Visit 8

Visit 8 will be performed 2 weeks (±2 days) following Visit 6 and the following assessments will be performed: an assessment of the injection sites, vital signs will be recorded, safety blood samples for haematology and biochemistry will be collected, urinalysis will be performed, a pharmacodynamic blood sample will be taken to measure antibody response and to obtain PBMCs to asses cellular responses, and AEs and concomitant medications will be reviewed.

Visit 9

Visit 9 will be performed 8 weeks (±2 days) following the first study vaccine administration and the following assessments will be performed: an assessment of the injection site and a pharmacodynamic blood sample will be taken to measure antibody response and AEs and concomitant medications will be reviewed.

Visit 10

A full medical examination will be performed 12 weeks (Day 85±2 days) following the first study vaccine administration and the following assessments will be carried out: an assessment of the injection site, a pharmacodynamic blood sample will be taken to measure antibody response, physical examination, vital signs, urinalysis, blood samples for haematology and biochemistry, serum pregnancy test and a review of AEs and concomitant medications. This visit signifies the endpoint for the primary endpoint for the study.

Safety Follow-Up (Visit 11)

A safety follow-up visit will be performed 6months (±2 weeks) following the second study vaccine administration to check the general health, measure vital signs, collect blood for haematology, biochemistry and to assess the immune response of the subject and to review adverse events (AEs).

Subjects do not have to use highly effective contraception following the Day 85 visit, should any subject become pregnant between Day 85 and Day 210, permission will be sought to follow the pregnancy, to obtain data on the outcome of the pregnancy.

12.3 Safety Assessments

The description of safety assessments is given below, and the timings of these assessments is given in the Schedule of Assessments. The time points of the safety assessments may change depending on information gained throughout the study, however the total number of safety assessments per subject will not be reduced, although unscheduled assessments may be performed at the discretion of the Investigator.

12.3.1 Clinical Laboratory Tests

The following parameters will be measured:

<u>Haematology</u>

Red blood cell count
Haemoglobin
Haematocrit
Platelet count
White blood cell count with absolute differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) counts

<u>Biochemistry</u>

Sodium
Potassium
Chloride
Bicarbonate
Blood urea
Creatinine
Creatine Kinase
Glucose
Calcium
Albumin
Cholesterol
C- reactive protein CRP
Triglycerides
Phosphorus (inorganic phosphate)
Lactate dehydrogenase (LDH)

Total protein
Globulin
Uric acid
Alkaline phosphatase (ALP)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyl-transferase (GGT)
Total bilirubin
Direct bilirubin

Urinalysis

Specific gravity
pH
Protein
Glucose
Ketone
Occult blood
Leukocyte esterase
Nitrites

Additional urine microscopy analysis will be undertaken, if any abnormalities are detected, to analyse for red blood cells, white blood cells, epithelial cells, bacteria, casts, and crystals.

12.3.2 ECGs and Vital Signs

Screening ECGs will be recorded after the subject has been lying for at least 5 minutes.

Vital signs will be recorded in the supine position, after the subject has been lying for at least 5 minutes. The normal ranges for vital signs are:

Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	40-90 mmHg
Pulse rate	40-100 bpm
Respiration rate	10-20 breaths per minute
Temperature	≥35.8°C and ≤37.5°C

12.3.3 Injection Site Tolerability Assessment

Injection site tolerability assessments will be performed as described in Appendix 1.

12.4 Time Windows for Visits

Vital signs will be performed within ±15 minutes of the scheduled time.

The time window for Visits 3 and 7 is ±2 hours.

The time window for Visits 4, 5, 6, 8, 9 and 10 is ± 2 days.

The time window for Visit 11 is ±2 weeks.

12.5 Safety Monitoring Board and Safety Data Review Meetings

Both cohorts will incorporate sentinel dosing of 2 subjects in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further subjects in that cohort will be

dosed until 24 hours after dosing the second subject, provided that there are no serious or unexplained safety issues as determined by the Investigator.

The decision to proceed with administration of the primary dose the subsequent cohort will be made as follows:

- It is intended that safety will be assessed after at least 24 evaluable subjects in cohort 1 (sentinel and main dose groups) have completed Visit 4 (Day 8), at which point the decision will be made to proceed with administration of the primary dose in cohort 2.

At least 24 evaluable subjects are required to complete through to visit 4 in cohort 1, in order to provide sufficient data for a decision to dose escalate. If the required number of evaluable subjects is not obtained in cohort 1, then the safety review committee (SRC) must decide whether there is enough information present to make a decision or whether further subjects should replace the dropped subjects or if sufficient information exists to determine if the dosing of cohort 2 is appropriate. The decision of the safety monitoring board and the output of the safety review must be clearly documented after the meeting.

The following safety data will be reviewed:

- Clinical Laboratory Tests
- Vital signs
- Assessment of injection site reactions
- AEs

The SRC will include at least two voting members - the Principal Investigator and Sponsor's Medical Monitor. If a voting member is unable to attend a Safety Data Review Meeting, a designated back-up can attend on their behalf and act as a voting member. Designated back-ups must be agreed and documented in advance. Non-voting members may also be part of the SRC.

The SRC will meet in person or by teleconference at scheduled Safety Data Review Meetings at which the safety data will be reviewed. A summary of safety data will be provided for review prior to these meetings for the SRC to review.

After review and discussion of all the data, the decision will be made on dose escalation and documented by signature of a Dose Escalation Approval Form by the voting members of the SRC. Minutes documenting the main points discussed and decisions made regarding dose escalation will be produced. The minutes will be agreed by all parties and filed in the site Trial Master File.

Progression to the next higher dose level will be stopped if any of the study stopping criteria are met as described in Section 12.7. Individual subjects will be discontinued from the study if they meet any of the individual subject stopping criteria as described in Section 12.6.

12.6 Individual Subject Stopping Criteria

Subjects who meet one or more of the following stopping criteria will receive no further doses of the study vaccine but will be followed up for safety:

- Severe injection site reaction, see Appendix 1
- Severe systemic reaction, e.g. anaphylaxis, see section 14.2.1
- Persistent febrile reaction (≥38.5°C for ≥12 hours) at the Investigator's discretion
- SAE related to the study agent

The medical safety of the subject is of paramount importance when discussing study continuation.

12.7 Study Stopping Criteria

A Safety Review Meeting will be convened to determine the progression of the study if any of the following scenarios occur:

- If one of the sentinel group or more than 20% of the subjects in a cohort experience a severe site reaction related to the GBS-NN/NN2 vaccine (study agent).
- If one of the sentinel group or more than 20% of the subjects in a cohort experience a severe systemic reaction related to the study agent.
- If one of the sentinel group or more than 20% of the subjects in a cohort experience a persistent febrile reaction (>38.5°C for ≥12hours) related to (study agent).
- If one or more subjects experience a SAE related to the study agent.
- If two or more subjects in the same cohort, experience 'severe' non-serious adverse reactions (i.e. severe non-serious adverse events, independent of system-organ-class, considered at least possibly related, to the IMP administration).

13. PHARMACODYNAMIC ANALYSIS AND ASSESSMENTS

13.1 Pharmacodynamic blood sample – antibody response

Each blood sample will be approximately 20 mL in volume, to yield approximately 10 mL of sera. The sera will be divided into aliquots, as described in the laboratory manual. Seven samples will be collected during the study which represents approximately 140 mL of blood.

The total blood volume taken over the study will be approximately 300 mL, which represents seven of approximately 20 mL pharmacodynamic samples, two of approximately 40 mL PBMC's and seven of approximately 9 mL clinical laboratory blood samples.

Pharmacodynamic samples will be collected at the following timepoints; Day 1, Day 15, Day 29, Day 43, Day 57, Day 85 and Day 210

Detailed processing instructions will be included in a separate lab manual.

[redacted]

Serum samples for PD antibody response analysis will be performed at [redacted] at [redacted] and [redacted]

Serum samples will be assayed in a validated ELISA to measure the concentrations of IgG specific for GBS-NN and GBS-NN2. Raw data from the assay will be inspected by the QC/QA scientists at the analytical lab to identify any samples which give unexpected results based on the normal kinetics of IgG induction following vaccination. Such unexpected values may indicate a problem with sample identification or with the assay performance. Potentially anomalous results will be discussed with the sponsor, without revealing the identity of the subjects, and if necessary samples will be re-analysed and corrected if the result fits with expectation. If the re-analysis returns essentially the same result a decision will be taken on whether to exclude the samples from the IG population analysis. Prior to formal statistical analysis of the results a standard test for outliers (e.g. the ROUT function in Grpahpad Prizm or equivalent) will be performed and any data points identified will be excluded from the analysis. In parallel the analysis will be performed on all data points including outliers to reveal the magnitude of the effect of excluding them.

14. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS ANDREPORTING

14.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An AE can be:

- Any unfavourable and unintended sign (including reactions from overdose, abuse, incorrect use of any treatment, or interaction)
- Any new disease or exacerbation of an existing disease (e.g. increase in frequency or worsening in nature)
- Any deterioration in measurements of laboratory values or other clinical tests (e.g. vital signs or X-ray) that results in symptoms, a change in treatment, or discontinuation from the IMP
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline
- Other medical events regardless of their relationship to the IMP, such as accidents, falls and any injuries resulting from them.

AEs will be recorded from the start of the study, i.e. from the first visit to the study unit on Day 1, until the post-study medical visit.

After completion of the 12-week period following the first vaccination (i.e. after Visit 10), AEs will be recorded by the subject in a diary card, and only those deemed to be relevant or significant by the Investigator will be recorded in the eCRF. A relevant or significant AE will be any event that caused the patient to visit any health care professional. These events will be recorded and the Investigator will determine if the event was possibly related to the investigational product. Any event deemed serious will be processed as a SAE in the normal way and if considered related reported as a SUSAR.

14.2 Categorisation of Adverse Events

14.2.1 Intensity Classification

AEs will be classified as mild, moderate or severe according to the following criteria:

Mild: Awareness of sign, symptom, or event, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

14.2.2 Causality Classification

The relationship of an AE to the study vaccine will be classified according to the following:

Related: A reaction that: follows a reasonable temporal sequence from administration of the vaccine, follows a known or expected response pattern to the suspected vaccine, could not be reasonably explained by the known characteristics of the subject's clinical state and, if necessary, the reaction returns on re-starting the vaccine (re-challenge).

Unrelated: A reaction that: does not follow a reasonable temporal sequence from administration of the vaccine and for which there is sufficient and conclusive information that the event is not related to the study vaccine.

14.3 Recording and Follow up of Adverse Events

Up to Day 85 (Visit 10), the subjects will be instructed to spontaneously report all AEs to the site staff or Investigator as soon as possible. Any AEs observed or reported by a subject and/or staff up to Day 85 (Visit 10) will also be recorded in the eCRF. The Investigator will review results from the physical examinations. All new and aggravated findings, as compared with baseline, must be identified and recorded as AEs in the eCRF. Following Day 85 (Visit 10) AEs will be recorded by the subject in a diary card, and only relevant or significant AEs will be recorded in the eCRF.

AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the Investigator must obtain adequate information to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. study vaccine or other illness). The Investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE, after the date of therapy discontinuation, is required if the AE or its sequelae persist. Any AE that is still ongoing at the post-study medical visit will have an outcome of 'ongoing' recorded in the eCRF, however the Investigator will continue to follow up ongoing related AEs and record information in the source documents. Related SAEs will be followed until the event resolves or the event or sequelae stabilise and this information will be reported to the Sponsor using the SAE reporting forms.

14.4 Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SAE is any AE that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

A SUSAR is an adverse reaction, which is both serious and unexpected.

14.5 Reporting Timelines

14.5.1 SAE Reporting

An SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period. Any SAE with a suspected causal relationship to the IMP occurring at any other time after completion of the study must be promptly reported.

Contact Details for SAE Reporting:

The following mandatory information must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Protocol number
- Subject number
- AE
- IMP
- Investigator's name and contact details

Causality assessment should be completed as soon as possible.

Follow-up information should be actively sought until the SAE has resolved or sequelae have stabilised. Additional information e.g. hospital reports or death certificates, may be requested by the Sponsor and should be anonymised/pseudonymised before transmission and subsequently filed in the Investigator Site File.

The expectedness of an SAE shall be determined by the Sponsor according to the most recent version of the Investigator's Brochure.

14.5.2 SUSAR Reporting

The Sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR), which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is reported as soon as possible to the MHRA, the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and the relevant Ethics Committee. This needs to be done not later than seven days after the sponsor was first aware of the reaction. Any additional relevant information should be sent within eight days of the report.

The Sponsor shall ensure that a SUSAR which is not fatal or life-threatening is reported as soon as possible and in any event not later than 15 days after the Sponsor is first aware of the reaction.

14.6 Abnormal Findings from Investigations or Assessments

Abnormal findings from investigations or assessments will be recorded as AEs if the Investigator considers they are clinically significant and/or result in medical intervention. This may include but is not limited to abnormal laboratory results, physical examination findings and vital sign

values/changes.

14.7 Pregnancy

Pregnancy is not an adverse event but the outcome of a pregnancy might be an adverse event. Over the course of the 6 month follow up it is possible that one or more subjects may become pregnant after day 85. It is important that any pregnancy is followed up. On being notified of a pregnancy the Investigator will complete a pregnancy notification form, which will be submitted to [redacted], and will inform the Sponsor. [redacted] will seek permission to follow up the pregnancy and at the time of the estimated date of delivery will contact the Investigator to remind the Investigator to determine the outcome of the pregnancy with the subject.

15. STATISTICAL EVALUATION

Details of the planned statistical analyses will be described in the Statistical Analysis Plan (SAP) and some important features are presented in this protocol. Statistical analyses will be performed by [redacted] using SAS version 9.3.

15.1 Statistical method description

15.1.1 General information

Demographic, baseline characteristics and data recorded during the study will be summarized using descriptive statistics by treatment (placebo or vaccine) and dose group, unless otherwise specified.

Individual data will be presented as a data listing, sorted by treatment and administered dose level.

For parameters with evaluation before vaccination and in case of re-checked value(s), only the last observation prior to dosing will be used in descriptive and inferential statistics and derivations of other parameter values. After vaccination, only values of scheduled assessments (planned in the protocol) will be used.

For laboratory/clinical parameters for which laboratory/reference ranges will be available, position of parameter values according to ranges will be flagged with the following rule:
- "L" for values lower than laboratory/reference ranges;
- "H" for values higher than laboratory/reference ranges.

In addition, parameter values can be assessed by investigator and flagged as follows in order to determine clinical relevance:
- Normal;
- Abnormal and NCS (Not clinically Significant);
- Abnormal and CS (Clinically Significant).

15.1.2 Descriptive statistics

Descriptive statistics for quantitative parameters will be provided using number of observations (N), Geometric mean, 95% confidence intervals, standard deviation (SD), minimum, median and maximum. Descriptive statistics for qualitative parameters will be provided using absolute frequencies (n) and relative frequencies (%). For immunological endpoints (IgG concentration and fold increase) geometric means with 95% confidence intervals for the geometric mean will additionally be presented.

15.1.3 Inferential statistics

Statistical tests will be carried out to compare results between treatment groups, depending on studied variable type. These analyses will be fully detailed in the SAP.

For categorical endpoints, such as local and systemic reactogenicity, a comparison of events intensity (scores) between groups can be performed with an adequate statistical test dealing with categorical variables (for example: Fisher exact test, Chi square test or generalized estimating equations).

For continuous endpoints, such as immune response induced by different GBS-NN/NN2 vaccine dosing regimens, appropriate statistical methods (for example: ANOVA or ANCOVA) can be used to compare pre-vaccination and post-vaccination levels as well as post-vaccination levels between groups.

15.2 Studied populations for each study part

The following populations will be taken into account for each study part:

- **Randomized Set (RAN)**: All included subjects who are randomized at V2 to one of the two cohorts;
- **Safety Set (SAF)**: All subjects from the SAF set who receive at least one dose of the study vaccine (or placebo) will be taken into account in the description of the population (demographic or baseline characteristics);
- **Immunogenicity Set (IG)**: The subset of subjects from the SAF set who will receive at least one dose of the study vaccine (or placebo) with available pre- and post-vaccination titres.
- **Per Protocol Set (PP)**: All subjects from the IG set who receive both doses of the study vaccine (or placebo) and provide evaluable samples for analysis of the IgG antibody response to the GBS-NN/NN2 vaccine at Day 85 (most important immunological endpoint) and do not violate the protocol.

The safety analyses will be performed on the SAF set. The immunological analyses will be performed on the IG set. The most important immunological endpoint (immune response on Day 85) will also be performed on the PP set if the number of subjects in the PP set differs by more than 5% from the number of subjects in the IG set.

Missing or incomplete data will not be replaced, unless otherwise specified (example: values strictly under the LLOQ for immunogenicity data).

15.3 Sample size

Up to 60 healthy female subjects will be included in 2cohorts of 30 subjects respectively.

15.4 Studied criteria

15.4.1 Characteristics of included subjects

- **Subject disposition**
  Subject disposition will be presented for the RAN set and will include the number enrolled, the number in each subject population for analysis (RAN, SAF, IG and PP), the number who withdrew prior to completing the study and primary reason for withdrawal (if applicable).

- **Subject demographic characteristics**
  For demography, continuous variables (for example: age, height, weight, BMI) and qualitative variables (for example: ethnic origin) will be summarized using descriptive statistics on the SAF population. Demographic characteristics will be also presented for other study populations (IG and/or PP) if they are different from SAF.

- **Medical history events**
  Medical and surgical history events will be coded using MedDRA (latest version) and will be summarized by System Organ Class (SOC) and Preferred Term (PT). Subjects will contribute only once per SOC and PT. In case of few relevant history events (≤5 per study part for example), only a listing will be provided according to treatment/dose group and subject.

- **Physical examination**
  Abnormal physical findings at screening period or at V2 pre-dose (study baseline) will be listed by treatment/dose group, subject and visit.

- **Pregnancy test**
  Serum pregnancy test will be performed at screening and post-study medical visit and urine pregnancy test will be performed prior to each administered dose (primary and booster doses at Visit 2 and Visit 6 respectively). A listing of positive results will be presented by treatment/dose group, subject and visit.

- **Previous medications**
  Previous medications will be listed and will be presented by treatment/dose group and subject.

- **Concomitant medication**
  Concomitant treatments will be listed by treatment/dose group.

15.4.2 Primary endpoint

The primary objective is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine for 12 weeks after the first dose of vaccine.

All the subjects included in the SAF set (including the withdrawal and dropout subjects) will be evaluated for safety analysis.

The following endpoints will be evaluated:

- **Local and systemic reactogenicity**

Assessment results will be described according to treatment/dose group and visit.

- **Adverse events**

Adverse events will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA, latest version). They will be classified into pre-defined standard categories according to chronological criteria:

Treatment Emergent Adverse Events (TEAEs): AEs which occur for the first time after the first administration or present before and worsened during vaccine exposure.

Non-Treatment Emergent Adverse Events (NTEAEs): AEs which occur before the first study vaccine administration (also called "pre-dose event").

TEAEs will be described by relation to study vaccine (for example: related or unrelated) and maximum intensity (for example: mild / moderate / severe) according to treatment/dose group. Descriptive statistics will be characterised by number of TEAEs, number and percentage of subjects with at least one TEAE (based on SAF). In case of few TEAEs (≤5 per study part for example), only a listing will be performed.

If descriptive statistics are performed, vaccine relation of TEAEs (*i.e.* related or not related to study vaccine) will be summarized by MedDRA codes (SOC and PT) and treatment/dose group.

Two distinct listings of TEAEs and NTEAEs will be presented by treatment/dose group, subject and MedDRA codes in order to provide more information about adverse events (example: description, duration, time since last administration if

applicable, seriousness, relation to study vaccine, any actions taken as concomitant medication or hospitalization).

- **Laboratory tests**

  Biochemistry and haematology tests will be performed at V1 (screening), V2, V4, V5, V8, post-study medical V10 and V11.

  Parameter values, position according to laboratory ranges (if available) and investigator assessment will be listed according to visit for each treatment/dose group. In order to assess study evolution of parameters after vaccination, parameter values changes from pre- to post-dose visits (baseline to pre second dose Day 29 (effect of first dose) and baseline and pre second dose to 28 days after second dose (Day 57) then base line to Day 85). will be calculated. Emergent values (for parameters with available laboratory ranges; values not within this range) with their corresponding position according to ranges will be listed by treatment/dose group and subject.

- **Urinalysis**

  Urinalysis will be performed at V1 (screening), V4, V8 and post-study medical visit V10.

  Parameter values (quantitative or binary results, *i.e.* positive/negative), position according to laboratory ranges (if available) and investigator assessment will be listed according to visit for each treatment/dose group. In order to assess study evolution of continuous parameters after vaccination, parameter values changes from screening to post-study medical visit will be performed. Emergent values (for parameters with available laboratory ranges or with binary results) will be listed by treatment/dose group and subject.

- **Vital signs**

  Vitals signs will be characterised by heart rate, blood pressure, oral temperature and respiratory rate. Vital signs will be assessed at V1 (screening), V2 (pre-dose, T2h and T4h post-dose), V3, V4, V5, V6 (pre-dose and T2h post-dose), V7, V8, and post-study medical V10 and V11.

  Parameter values, position according to reference ranges (if available) and investigator assessment will be described according to visit and assessment time for each treatment/dose group. In order to assess study evolution of parameters after vaccination, parameter values changes from pre-dose to post-dose assessments will be performed. Emergent values (for parameters with available reference ranges; values not within this range) with their corresponding position according to reference ranges will be listed by treatment/dose group and subject.

- **12-lead ECG parameters**

  ECGs will be assessed at V1 (screening).

  Parameter values, position according to reference ranges and investigator assessment (if available) will be described according to visit for each treatment/dose group. Emergent values (for parameters with available reference ranges; values not

within this range) with their corresponding position according to reference ranges will be listed by treatment/dose group and subject.

- **Physical examination**

  Abnormal physical examinations recorded at post-study medical visit V10 andV11 will be listed according to treatment/dose group and subject.

15.4.3 Secondary Endpoints (Immunological Endpoints)

The secondary objectives are:

- To evaluate the IgG antibody response to the GBS-NN/NN2 vaccine at Day 85 (most important immunological endpoint).
- To assess whether pre-existing antibody levels affect the vaccine-induced antibody response.

Immunological parameters measured to evaluate objectives

In order to evaluate these objectives, GBS-NN and GBS-NN2 specific IgG concentrations will be determined by ELISA against a reference standard human antibody preparation of known concentration as described in the laboratory protocol and used to derive the following parameters for each subject:

- Antibody concentrations specific for GBS-NN and GBS-NN2 at each sample point (μg/mL)
- Fold increases over pre-immunisation level (Day 1) in antibody concentrations at each sample point (ratio)

Specific Endpoints calculated from immunological parameters

These parameters will be used to derive the following endpoints at all time-points according to the treatment group:

- Geometric mean antibody concentrations specific for GBS-NN and GBS-NN2inμg/mL (with 95% CI).
- Geometric mean fold increase in antibody concentration (with 95% CI).
- Seroconversion rate (proportion of subjects with fold increase above threshold at any time point post vaccination up to Day 85).
- Proportion of subjects achieving antibody concentrations above specific thresholds at Days 29 & 85 (these will be 2, 4, 8 μg/mL). This will provide an assessment of the immune response to the first and second doses.

The most important immunological end point will be the values of these end points at Day85, 12weeks after the administration of the first dose of vaccine.

15.4.4 Exploratory endpoints

Exploratory Objectives

Endpoints to be measured to assess the exploratory endpoints:

- 

16. ETHICS AND REGULATORY

16.1 Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and Contract Research Organisation(CRO), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

1. Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Patients"), and all its accepted amendments to date concerning medical research in humans.
2. ICH E6 Guideline for GCP and subsequent notes for guidance (CPMP/ICH/135/95) European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).
3. European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.
4. GCP Directive 2005/28/EC.

This study will be conducted in accordance with national and local laws (e.g. drug and narcotics laws) of the countries where study sites are located.

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH Good Clinical Practice to which the protocol conforms as well as all governing local regulations and principles for medical research.

16.2 Review

The protocol, any protocol amendments, subject information sheet (VIS), informed consent form (ICF) and any study related information or documents issued to subjects will be reviewed and approved along with other required documents by the Ethics Committee (EC) and each study site's local EC before subjects are screened for entry. The ECs should be constituted and functioning in accordance with ICH E6, Section 3.2, and any local regulations. The EC that provides a positive opinion for this study will be included in the clinical study report for this protocol.

A signed letter of positive opinion regarding the study from the EC Chairman must be sent to the Investigator who will provide the Sponsor with a copy. The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the EC of any reportable AEs per ICH guidelines and local EC standards of practice.

SAEs should be reported to the EC in accordance with local regulatory requirements.

In the case of early termination/temporary halt of the study, the Investigator should notify the EC and the Sponsor should notify the Competent Authority (CA) within 15 days and a detailed written explanation of the reasons for the termination/halt should be given. If the EC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the EC to the Sponsor.

At the end of the study, the EC and CA will be notified within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The Sponsor will always also provide the EC/CA with a summary of the study's outcome.

16.3 Subject Information and Informed Consent

Informed consent should be obtained by means of a VIS and ICF, prepared in accordance with ICH E6 (R2) Section 4.8.10 and applicable local regulations, written in non-technical language. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

Prior to study start, the subjects will receive a full explanation of the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the VIS and ICF before signing and dating the ICF. The Investigator or qualified person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

The original signed ICF for each subject will be verified by the Sponsor monitors and kept in the study centre investigational site files.

17. GENERAL OBLIGATIONS, AGREEMENTS AND ORGANISATION

17.1 Data Protection and Confidentiality

Data protection will be carried out in accordance with the Principles of the General Data Protection Regulation. This will apply to all study data in whatever format it is collected and recorded.

17.2 CRFs and Handling

Electronic CRFs will be used in this trial. Should any corrections or amendments be necessary, data clarification requests will be forwarded to the Investigator or designee.

17.3 Quality Control and Monitoring

The conduct of the study will be monitored by appropriately qualified staff from the Sponsor and/or an organisation authorised to conduct activities on the Sponsor's behalf. Risk based monitoring will be used. For further specifications please refer to the monitoring plan. The Sponsor will retain the responsibility for monitoring and may delegate this responsibility via a contract and/or Monitoring Manual.

The study will be monitored at regular intervals and the frequency of monitoring visits will be determined by the rate of subject recruitment. The following will be reviewed at these visits:

- Responsibilities of the Investigator and the study site under GCP requirements
- Compliance with the protocol
- Consent procedure
- Source Data Verification (SDV)
- Procedures for AEs
- Storage and accountability of study vaccine

The purpose of SDV is to verify, so far as is possible, that the information in the CRF reflects the data recorded in the subject's source data records. SDV will be performed with due regard for subject confidentiality. SDV will be undertaken on an ongoing basis as part of the monitoring visits. Direct access to the source documents will be required. The monitor will make a direct comparison with data entered in the subject CRFs and the source data.

The Investigator must permit the monitor, the Sponsor's internal auditors and representatives from the Regulatory Authorities to inspect all study-related documents and pertinent source data records for confirmation of data contained within the CRFs.

17.4 Quality Assurance, Audit and Inspection

This study may be subject to audit by the CRO, Sponsor or their representatives and Regulatory Authorities. These audits may be undertaken to check compliance with the requirements of GCP and can include:

- In-house study file audit
- Audit of computer database
- Audit of Clinical Study Report

- Audit of selected study sites, requiring access to subject medical records, study documentation and facilities, laboratories or pharmacies used for the study.

The study site, facilities and all data (including source data) and documentation will be made available for audit by the Investigator according to the ICH-GCP guidelines. The Investigator agrees to co-operate with the auditor during his/her visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

In the event that a Regulatory Authority informs the Investigator that it intends to conduct an inspection, the Sponsor must be notified immediately.

17.5 Storage of Study Documents

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol, copies of CRFs, Investigator's Brochure, regulatory agency registration documents, ICFs, and EC correspondence.

The site will retain study documents for 15 years after completion of the study. This will include copies of the CRF. At the end of the 15-year period the site will contact the Sponsor who will determine any future arrangements for the storage of the study documents.

All CRFs and clinical trial data will be stored by the Sponsor or designee for a period of at least 15 years after termination of the study. The subject consent forms and re-identification lists will be archived with the Investigator for at least 15 years after termination of the study.

17.6 Registration and Publication of Study and Results

The trial will be registered by the Sponsor on a publicly accessible database e.g. http://www.controlled-trials.com.

The trial results will not be published without written consent by the Sponsor. Any oral or written communications /publications concerning the trial results will be reviewed and approved in writing by the Sponsor, which has a 60-day period to respond after receipt of the proposed communication/publication.

18. SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Assessments

	Screening Period	Treatment Period								Post-Study Medical	Safety Follow-Up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Assessment	Day -28 to Day -1	Day 1	Day 2	Day 8	Day 15	Day 29	Day 30[e]	Day 43	Day 57	Day 85	Day 210
Informed Consent	X										
Inclusion/ Exclusion Criteria	X										
Demography	X										
Medical History	X										
Physical Examination[d]	X	X				X[d]				X	
Height, Weight, BMI	X										
Vital signs[a]	X	X[b]	X	X	X	X[b]	X	X		X	X
12-lead ECG	X										
Urinalysis	X			X				X		X	
Safety laboratory tests	X	X		X	X			X		X	X
HIV, Hep B and Hep C	X										
Pregnancy test[c]	X	X				X				X	
Alcohol urine test	X	X									
Drugs of abuse test	X	X									
Review of subject eligibility		X									
Randomisation		X									
Administration Investigational vaccine		**X**				**X**					
PD blood sample – antibody response		X			X	X		X	X	X	X
PD blood sample – PBMCs		X						X			
Assessment of injection site		X	X	X	X	X	X	X	X	X	
AE check		X								X	X
Con med check	X	X								X	X

Footnotes

a. Heart rate, blood pressure, oral temperature and respiration rate.
b. Vital signs at dosing Visit will be recorded pre-dose and at 2 and 4 hours post-dose.
c. Serum pregnancy test at screening and post-study medical. Urine pregnancy test prior to each dose.
d. Targeted medical examination (including assessment of the injection site(s) to determine eligibility for discharge at least 4 hours post-dose
e. Photographs may be taken of injection site reactions as required.

19. REFERENCES

1. Baker C (2000) Group B streptococcal infections In Stevens DL, Kaplan EL eds. Streptococcal infections. NEW York (NY) Oxford University Press. 2000: 222-37
2. Madhi SA, Cutland CL, Jose L et al (2016) 'Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial.', Lancet Infect Dis, 16(8), pp. 923-934.
3. Donders GG, Halperin SA, Devlieger R et al (2016) 'Maternal Immunization With an Investigational Trivalent Group B Streptococcal Vaccine: A Randomized Controlled Trial.', Obstet Gynecol., 127(2), pp. 213-221.
4. Heyderman RS, Madhi SA, French N et al (2016) 'Group B streptococcus vaccination in pregnant women with or without HIV in Africa: a non-randomised phase 2, open-label, multicentre trial.', Lancet Infect Dis., 16(5), pp. 546-555.
5. Centre for Disease Control and Prevention (2002). Prevention of perinatal Group B streptococcal disease MMWR, 51:1-22
6. El Helali N, Nguyen JC, Ly A. et al., (2009) Diagnostic accuracy of a rapid real-time polymerase chain reaction assay for universal intrapartum group B streptococcus screening. Clin. Infect. Dis. Aug 1, 49: 417-23
7. Gravekamp et al., (1996), 64,3576
8. Gravekamp et al., (1997) 65,5216
9. Heath PT, Balfour GF, Tighe H, Verlander NQ, Lamagni TL, Efstratiou A (2009). Group B streptococcal disease in infants: a case control study. Arch. Dis. Child. 94(9) 674-680.
10. Heath PT, Balfour GF, Weisner AM et al., (2004) Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet 363 (9405), 292-294.
11. Anderson BL, Simhan HN, Simons KM, et al. Untreated asymptomatic group B streptococcal bacteriuria early in pregnancy and chorioamnionitis at delivery. Am J Obstet Gynecol 2007;196;524.e1-524.e5.
12. Thomsen AC, Mørup L, Hansen KB. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. Lancet. 1987 Mar 14;1(8533):591-3
13. Jordan HT, Farley MM, Craig A et al., (2008) Revisiting the need for vaccine prevention of late onset neonatal group B streptococcal disease: a multistate, population-based analysis. Pediatr. Infect. Dis. J. 27(12): 1057-1064.
14. KWS BioTest: MNV008-4-AM1. Evaluation of magnitude and kinetics of responses to "human doses" in mice and the need for alum. 28 Aug 2014.
15. KWS BioTest MNV002-4. Evaluation of NN protein as a putative vaccine for Group B streptococcal infection: protection from neonatal infection. 22 Oct 2012.
16. KWS BioTest: MNV003-5. Evaluation of NN protein as a putative vaccine for Group B streptococcal infection: neutrophil killing assessment. 28 Mar 2013.
17. KWS BioTest: MNV007-4. Evaluation of NN protein as a putative vaccine for A909 Group B streptococcal infection: protection from neonatal infection. 22 Oct 2012
18. Larsson, CE (2006) Association between low concentrations of antibodies to protein alpha and Rib and invasive neonatal group B streptococcal infection. Arch Dis. Child Fetal Neonatal, F403-F408.
19. Lin et al. Level of Maternal IgG Anti–Group B Streptococcus Type III Antibody correlated with protection of neonates against Early---Onset Disease caused by this pathogen.J.Infect.Dis.2004;190:928
20. Melin P, Schmitz M, Tsobo C et al.,(2000). Rapid intrapartum test (Stept B OIA) and prenatal cultures for identification of group B streptococcal carriers at delivery: a prospective study. In American Society of Microbiology(Ed) Program and Abstracts of the 40th Intersciences Conference on Antimicrobial Agents and Chemotherapy (p145 No 357 session 30) Washington. USA: American Society for Microbiology (ASM).

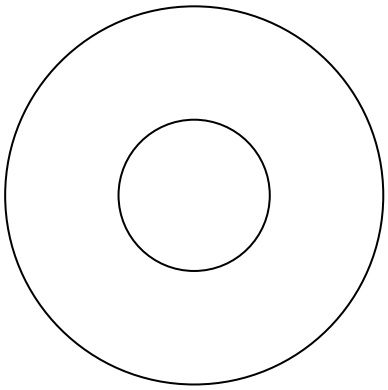
http://hdl.handle.net/2268/36477
21. Nizet V Ferrieri P, Reubens CE (2000) Molecular pathogenesis of group B streptococcal disease in newborns. In Stevens DL, Kaplan EL eds. Streptococcal infections. NEW York (NY) Oxford University Press. 2000: 180-221.
22. Schrag SJ, Zywicki S, Farley MM et al., (2000). Group B Streptococcal disease in the era of intrapartum antibiotics. N. Engl. J. Med. 342(1), 15-20.
23. Skoff TH, Farley MM, Petit S et al., (2009). Increasing burden of invasive group B streptococcal disease in non-pregnant adults 1990-2007. Clin. Infect. Dis., 49(1), 85-92.
24. Stahlhammar-Carlemalm (2007) Cell Host and Microbe, 427-434.
25. Verani JR, Schrag SJ (2010) Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin. Perinatol, 37: 375-92.
26. Zangwill KM, Schuchar A, Wenger JD (1992) Group B streptococcal disease in the United States, 1990, report from a multistate active surveillance system. MMWR CDC Surveil. Summ., 41(6):25-32

APPENDIX 1

INJECTION SITE TOLERABILITY ASSESSMENT

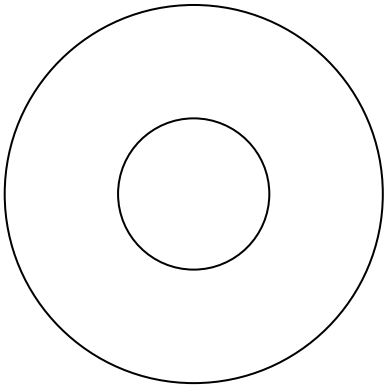
Tolerability assessments will be performed by a member of the clinical staff. An additional assessment by a physician will be made in the event of a local reaction being evaluated as moderate or severe. All measurements (in cm) refer to the longest dimension.

Redness



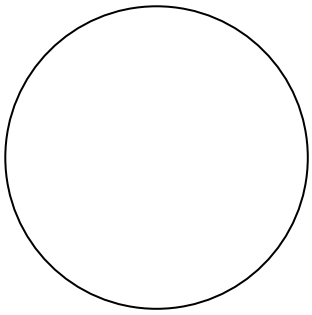
Grade	Description:	
0	NONE	No visible redness
1	MILD	Greater than 0 to 2 cm (incl.) redness
2	MODERATE	Greater than 2 to 5 cm (incl.) redness
3	SEVERE	Greater than 5 cm redness

Bruising



Grade	Description:	
0	NONE	No visible bruising
1	MILD	Greater than 0 to 2cm (incl.) bruising
2	MODERATE	Greater than 2 to 5cm (incl.) bruising
3	SEVERE	Greater than 5cm bruising

Induration



Grade	Description:	
0	NONE	No swelling detected
1	MILD	Palpable "firmness" only
2	MODERATE	Less than or equal to 4 cm swelling
3	SEVERE	Greater than 4 cm swelling

Itching

Grade	Description:
N:	ABSENT
Y:	PRESENT

Pain

Subjects will be asked if they experience any pain. If the answer is yes, they will be asked to rate the level of pain on a scale of 1-10. Assessment of pain will commence after first injection.

Any other local reaction (for example: necrosis or ulceration)? Please specify