Protocol MVX13211

A two-part, Phase I, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of a dose range of Group B Streptococcus vaccine (GBS-NN) in healthy female volunteers aged 18 to 40.

Version:	6.0
Version Date:	30 Nov 2015
EUDRACT Number:	2014-004542-10
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. PROTOCOL REVISION HISTORY

Date	Description
02 Mar 2015	Final Protocol v1.0
04 Mar 2015	v2.0 protocol updated to include diary cards for AE collection after Day 85 in Part B and addition of injection site assessment at discharge on Days 1 and 29.
16 April 2015	3.0 protocol clarified regarding maximum dose being 250 μg and the optional cohort 7 to investigate doses below 250 μg
27 May 2015	v4.0 protocol clarified regarding drugs of abuse and alcohol breath test at screening and urinalysis tests during study.
06 Oct 2015	v5.0 updated to change post dose medical cover and in house stay on day 1 and day 29 (if applicable) for Part B. Change in safety laboratory for Part B. TDL added to list of providers. Allocation of replacement randomisation numbers in Part B clarified.
30 Nov 2015	v6.0 updated to amend the time windows after Day 85 to +/- 3 weeks and to change the name of Huntingdon Life Sciences to Envigo.

2. STUDY CONTACTS

PRINCIPAL INVESTIGATOR

INVESTIGATIONAL SITE

24 HOUR SPONSOR MEDICAL MONITOR

SAFETY REPORTING

SAFETY LABORATORIES

[redacted]

[redacted]

STATISTICS, DATA MANAGEMENT AND REPORT WRITING

[redacted]

ANALYSIS OF PHARMACODYNAMIC BLOOD SAMPLES AND SWABS

[redacted]

3. SYNOPSIS

Protocol Number:	MVX13211
Study Vaccine(s):	Group B Streptococcus Vaccine (GBS-NN)
Title:	A two-part, Phase I, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of a dose range of Group B Streptococcus vaccine (GBS-NN) in healthy female volunteers aged 18 to 40.
EudraCT Number:	2014-004542-10
Objectives and Endpoints:	**Primary Objective** The primary objective is to evaluate the safety and tolerability of the GBS-NN vaccine for 12 weeks after the first dose of vaccine. The following endpoints will be evaluated to support this objective: local and systemic reactogenicity; adverse events; laboratory tests; urinalysis; vital signs; 12-Lead ECG parameters; physical examination. **Secondary Safety Objectives** The secondary safety objective for Part B is to evaluate the long term safety profile of the GBS-NN vaccine up to 1 year following the first dose. The same endpoints will be evaluated as for the primary objective. **Secondary Immunological Objectives** The secondary immunological objectives for both parts of the study are: • To evaluate IgG antibody responses induced by different vaccine doses alone or in the presence of Alhydrogel over time in healthy female volunteers. • To determine the impact of pre-existing antibody levels on the vaccine-induced antibody response. In addition for Part A: • To determine the effect of Alhydrogel® adjuvant on the immunogenicity of GBS-NN vaccine. • To select the dose levels and regimens for vaccination of cohorts in Part B, based on the antibody levels at 8 weeks following the first dose (Day 57). In addition for Part B:

	• To evaluate the immune response to the GBS-NN vaccine up to 1 year following the first dose. The following endpoints will be evaluated by group and time-point to support these objectives: • Geometric mean antibody concentration in µg/mL. • Geometric mean fold increase in antibody concentration. • Seroconversion rate (proportion of volunteers with fold increase above threshold). • Proportion of volunteers achieving antibody concentrations above specific thresholds at Day 85 (for Part A these will be 0.5, 1, 2, 4, 8 µg/mL and for Part B these may be modified based on the results from Part A). The primary immunological endpoints for both Part A and Part B will be the values of these endpoints at Day 85, 12 weeks after the administration of the first dose of vaccine. [redacted] • [redacted]
Study Design:	A Phase I, randomised, double-blind, placebo-controlled, parallel group, single centre study. All cohorts in Part A will incorporate sentinel dosing of 2 volunteers in

	each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further volunteers in that cohort will be dosed until at least 24 hours after dosing the second volunteer, provided that there are no serious or unexplained safety issues as determined by the Investigator. In Part A, the decision to proceed with administration of the primary dose in subsequent cohorts will be made as follows: • Safety will be assessed after Visit 4 (Day 8) for cohort 1, at which point the decision will be made to proceed with administration of the primary dose in cohorts 2 and 3. • Safety will be assessed after Visit 4 (Day 8) for both cohorts 2 and 3, at which point the decision will be made to proceed with administration of the primary dose in cohorts 4 and 5. • Safety will be assessed after Visit 4 (Day 8) for both cohorts 4 and 5, at which point the decision will be made to proceed with administration of the primary dose in cohort 6. In Part B, sentinel dosing is not required, and volunteers in all groups may be randomised and dosed concurrently.
Study Duration:	In Part A, each individual volunteer will be involved in the study for approximately 12 weeks (excluding the 28 day screening period and the 6 month safety follow up phone call). The start of the study is defined as check-in on Day 1. In Part B, each individual volunteer will be involved in the study for approximately 1 year (excluding the 28 day screening period). The start of the study is defined as check-in on Day 1.
Study Population:	In Part A, up to 70 healthy female volunteers aged 18 to 40 will be randomised (i.e. up to 7 cohorts of 10 volunteers). In Part B, up to 240 healthy female volunteers aged 18 to 40 will be randomised (i.e. 3 cohorts of 80 volunteers). The final number of volunteers to be randomised in Part B will be calculated following a review of the data from Part A, and will not exceed 240 volunteers.
Investigational Medicinal Product and mode of administration	[redacted] [redacted] Administration will be by intramuscular injection, preferably into the non-dominant arm. The dominant arm may be used if it is not possible to administer into the non-dominant arm e.g. due to an ongoing injection site reaction, or tattoo.
Selection of Doses	Based on the data derived from dose ranging studies in mice it is considered appropriate to commence dosing at 10 µg in humans. [redacted]

[redacted]

It is currently anticipated that the following strategy will be employed, however this may be modified:

Part A:

Three dose levels will be selected, with and without Alhydrogel®: A, B, and C (where A is the lowest dose and C is the highest dose). It is anticipated that these doses will be 10µg, 50µg and 250µg, although these may be modified following ongoing review of data by the Safety Review Committee. The dose increase between cohorts will not exceed a five-fold increase.

It is anticipated that each cohort will receive the following dose regimen as described in the table below.

Note that cohort 7 is an optional cohort, and will proceed if deemed necessary to test an additional dosing regimen at a dose level below 250 µg, which will be determined following an ongoing review of the data.

Cohort	Dose schedule	Dose level	Adjuvant
1	Day 1, 29	10µg (A)	None
2	Day 1, 29	50µg (B)	None
3	Day 1, 29	10µg (A)	Alhydrogel®
4	Day 1, 29	250µg (C)	None
5	Day 1, 29	50µg (B)	Alhydrogel®
6	Day 1, 29	250µg (C)	Alhydrogel®
7	TBD	TBD, not exceeding 250 µg	TBD

Anticipated dose regimens in Part A

Part B:

It is anticipated that the results from Part A will reveal where the optimal dose is likely to lie.

Three dose regimens will be selected for evaluation in Part B. At least two dose levels will be evaluated, which may be the same or different to those administered in Part A, but will not exceed the highest dose administered in Part A. It is anticipated that the regimens in Part B will comprise two doses of Alhydrogel® adjuvanted vaccine with the second being administered after a variable interval, not exceeding four weeks, it is, however, possible that a single dose, of vaccine without Alhydrogel®

	may be evaluated in Part B.
Treatment Schedule for Part A:	Volunteers will provide written informed consent and will be screened for eligibility within 28 days before first study vaccine administration (Day 1). Eligible volunteers will receive one of up to 7 dosing regimens of GBS-NN or placebo on 1 or 2 occasions – a primary dose will be administered on Day 1, and if a booster dose is required, this will be administered 4 weeks later, although this time interval may change if the dosing regimen is changed. There will be 10 volunteers in each group, 8 randomised to active and 2 to placebo. All cohorts in Part A will incorporate sentinel dosing of 2 volunteers in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further volunteers in that cohort will be dosed until at least 24 hours after dosing the second volunteer, 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 subsequent cohorts will be made as described in the Study Design section. During the study, volunteers will attend study visits as described in the Schedule of Assesments, up to the post-study medical visit at Day 85. Safety assessments will be performed and pharmacodynamic blood samples will be collected at study visits according to the Schedule of Assessments. [redacted] A safety follow-up phone call will be performed 3 months after the end of the study i.e. 6 months following the first study vaccine administration to check the general health of the volunteer and to review adverse events (AEs).
Treatment Schedule for Part B:	Volunteers will provide written informed consent and will be screened for eligibility within 28 days before first study vaccine administration (Day 1). Eligible volunteers will receive one of 3 dosing regimens (X, Y or Z) of GBS-NN or placebo on 1 or 2 occasions – a primary dose will be administered on Day 1, and if a booster dose is required, this will be administered 4 weeks later. There will be up to 80 volunteers in each group, up to 60 randomised to active vaccine and up to 20 to placebo. During the study, volunteers will attend study visits as described in the Schedule of Assessments, up to the post-study medical visit at Day 365. Safety assessments will be performed, vaginal and rectal swabs will be performed and pharmacodynamic blood samples will be collected at study visits according to the Schedule of Assessments. [redacted]
Statistical Analysis:	Details of the planned analyses will be described in the SAP and some (but not all) important features are listed below and presented in the protocol statistical part: **<u>Studied criteria for the two study parts</u>**

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

- Demographic and baseline data;
- Safety data including:
  - vital signs (heart rate, blood pressure, tympanic temperature and respiratory rate)
  - 12-lead ECG
  - safety laboratory tests (haematology, biochemistry)
  - urinalysis
  - adverse events
  - physical examinations
  - assessment results of the injection site (local reactogenicity) and systemic reactogenicity using scale variables;
- Pharmacodynamic blood sample results (antibody response).

[redacted].

Descriptive statistics

Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum. Descriptive statistics for qualitative parameters will be provided using absolute frequencies (n) and relative frequencies (%).

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 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 vaccine dosing regimens, appropriate statistical method (for example: ANOVA) can be used to compare pre-vaccination and post-vaccination levels.

Studied populations

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

- **Intention to Treat Set (ITT)**: All included volunteers who receive at least one dose of the study vaccine will be taken into account in the description of the population (disposition, demographic or baseline characteristics);
- **Immunogenicity Set (IG)**: The subset of volunteers who will receive at least one dose of the study vaccine with available pre- and post-vaccination titers.
- **Per Protocol Set (PP)**: All volunteers who receive both doses of the study vaccine and provide evaluable samples for analysis of the

	[redacted] The Primary and Secondary Safety analyses will be performed on the ITT set. The Secondary Immunological analyses will be performed on the IG set. The "primary" immunological analysis (i.e. the results on Day 85 in both study parts) will also be performed on the PP set. **Sample size:** Up to 70 healthy female volunteers in part A (7 cohorts of 10 volunteers) and up to 240 in part B (3 cohorts of 80 volunteers). The final number of volunteers to be randomized in part B will be calculated following a data review from part A.

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
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
ITT	Intention to Treat

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
PT	Preferred Term
SAE	Serious Adverse Event
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 Volunteering Prevention System
VIS	Volunteer Information Sheet
WHO-DD	World Health Organisation – Drug Dictionary

6. INTRODUCTION

6.1 Background

Streptococcus agalactiae is a Lancefield Group B Streptococcus (GBS), first isolated in 1887, but was not considered a human pathogen until the 1970's. This bacterium has now emerged as the leading cause of neonatal sepsis. GBS 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).

GBS is a human commensal of the gastrointestinal tract and about 10 to 35% of pregnant women are carriers. GBS colonisation can be transient, intermittent or persistent and yet commonly asymptomatic (Verani and Schrag 2010). Spontaneous vaginal/rectal colonisation constitutes the fundamental risk factor for GBS transmission. Other recognised risk factors include, preterm birth (less than 37 weeks), a mother with a previous baby infected with GBS, presence of high temperature during labour, over 18 hours rupture of membranes, and the presence of GBS in urine of a pregnant woman.

Introduction of inter partum antibiotic prophylaxis (IAP) in 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 any way 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 lead 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 exist for the development of an effective alternative to IAP for the prevention of neonatal GBS infections, as outlined above.

Maternal 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 likely protect both 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.

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). Indeed, CPS-based vaccines

are frequently used for targeting Gram positive bacteria, and two CPS-based vaccines are currently in development for prevention of GBS infections. However, a CPS-based vaccine needs to contain individual CPS components from each of the clinically relevant serotypes in order to obtain sufficient coverage. For GBS, this would require adding a minimum of 5 serotypes (Ia, Ib, II, III and V), and the leading CPS-based vaccine candidate in development today only contains 3. The need to include multiple CPS components, combined with the need to conjugate the CPS to protein carries in order to make them sufficiently immunogenic, makes CPS-based vaccines rather complicated and expensive to make compared to a single protein vaccine capable of covering the same set of serotypes.

Minervax is developing the GBS-NN vaccine candidate that consists of a fusion protein containing the two N-terminal regions of the Rib and AlphaC proteins. Like for CPS, naturally occurring antibodies against the full-length Rib and AlphaC proteins are found in pregnant women, and such antibodies are efficiently transferred to their babies in-utero. Importantly, a correlation between high levels of such antibodies in the mothers and their children are associated with increased protection against invasive GBS disease in the new- borns. Finally, Rib and AlphaC elicit protective immunity in animal models when administered with alum, an adjuvant accepted for human use (Larsson et al., 1999). A vaccine based on the Rib and the AlphaC proteins therefore offer an alternative to a CPS- based vaccine.

The N-terminal regions of the Rib and AlphaC have been found to elicit a potent and protective immune response against GBS, which is even more potent than the immune response induced by the rest of the Rib and AlphaC proteins (Gravekamp et al. 1996 Vol 64, Gravekamp et al. 1997 Vol 65, Stålhammar-Carlemalm et al., 2007). As a consequence a vaccine based on a fusion protein consisting of the two N-terminal domains of Rib and Alpha C was selected as the vaccine candidate.

The GBS-NN fusion protein has been found to [redacted] protect adult mice against lethal challenges with prototype strains of serotypes Ia, Ib, II, and III following direct vaccination (Stålhammar-Carlemalm et al., 2007). [redacted]

Given that GBS-NN has been found to be [redacted] rotect against infections with serotypes Ia, Ib, II, III and V. And taken together with the finding that high levels of naturally occurring antibodies against Rib and AlphaC [redacted] correlate with protection against invasive GBS disease in newborns, makes GBS-NN an ideal candidate for a GSB vaccine with an estimated coverage of 95% of clinical isolates and hence justifies clinical testing of the vaccine.

[redacted]

Based on the data derived from the dose ranging studies in mice, it is considered appropriate to commence dosing at 10µg in humans. [redacted]

The present study will also investigate whether adding the adjuvant Aluminium hydroxide (Alhydrogel®) will improve the immune response, and this will be done in parallel with dosing of GBS-NN.

It is anticipated that dose escalation will occur with a five-fold increment. Dose escalation will only occur after review of safety data up to two weeks after vaccination. At this review a decision will also be made whether a booster dose is required (may be given 28 days after first vaccination).

In Part A, the first cohort will consist of 10 volunteers (8 active, 2 placebo) to receive a dose of 10µg without Alhydrogel®, the second and third cohorts may be dosed in parallel. Cohort 2 will receive a dose of 50µg, without Alhydrogel® and cohort 3 will receive 10µg GBS-NN with Alhydrogel®. Cohorts 4 and 5 may also be dosed in parallel with 250 µg without Alhydrogel® in cohort 4, whilst cohort 5 will receive 50µg with Alhydrogel®. The 6th cohort will receive 250µg GBS-NN with Alhydrogel®.

It is anticipated that the results from Part A will reveal where the optimal dose is likely to lie, and three dose regimens will be selected for evaluation in Part B. In Part B, each cohort will consist of 80 volunteers (60 active, 20 placebo)

It is expected that data accrued from the present study will allow the selection of the most appropriate dose to elicit the best immune response in humans. This dose will then be tested in pregnant women in subsequent studies with an expectation of 95% cover of GBS serotypes compared with 70% achieved with other vaccines.

6.2.1 Rationale for Exploratory Immunological Assessments

[redacted]

[redacted]

[redacted]

6.3 Risk/Benefit Assessment

Antibodies against both full-length Rib and Alpha proteins, [redacted] as well as antibodies reactive with the GBS-NN vaccine candidate, 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 both 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.

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 vaccine is adsorbed with a known adjuvant, Alhydrogel, (0.5 mg of Al^{3+} per dose), corresponding to the dose used in many other commercial vaccines. Volunteers will receive maximum of 2 dosing occasions in the clinic. The initial Phase I trial will include up to 310 healthy adult women using contraceptives – Part A enrolling up 70 women and Part B enrolling up to 240 women. The vaccine will be given by the intramuscular route as was done in the animal safety studies. The Phase I trial will evaluate ascending dose levels of GBS-NN with and without Alhydrogel®.

A number of preclinical studies have been conducted in rats, rabbits and mini pigs. [redacted]

Initial safety and immunogenicity evaluation of escalating dose levels will select an appropriate dose for further evaluation in the target population of pregnant women to investigate if immunisation of pregnant women with GBS-NN can result in detectable IgG antibodies in the neonate that might provide protection to the new-born infants. [redacted] Thus doses of 10μg, 50μg and 250μg to be used in the present study will remain within the safety margins, and no overdosage is expected.

The normal adverse event profiles from Phase I studies suggest that a typical array of minor clinical study symptoms may be experienced by volunteers taking part in the study. GBS-NN has not previously been tested in human volunteers, although it is known that naturally occurring antibodies, reactive against the GBS-NN are found in pregnant women; the possibility of as yet unknown side effects should remain a consideration. The protocol requires that volunteers 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 volunteers in the study. GBS-NN, 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, 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.

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

GBS-NN should not currently be given to women known, or suspected to be, pregnant, or to nursing mothers. Currently GBS-NN 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.

All study volunteers 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.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

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

The following endpoints will be evaluated to support this objective: local and systemic reactogenicity; adverse events; laboratory tests; urinalysis; vital signs; 12-Lead ECG parameters; physical examination.

7.2 Secondary Safety Objectives

The secondary safety objective for Part B is to evaluate the long term safety profile of the GBS-NN vaccine up to 1 year following the first dose.

The same endpoints will be evaluated as for the primary objective.

7.3 Secondary Immunological Objectives

The secondary immunological objectives for both parts of the study are:

- To evaluate IgG antibody responses induced by different vaccine doses alone or in the presence of Alhydrogel over time in healthy female volunteers.
- To determine the impact of pre-existing antibody levels on the vaccine-induced antibody response.

In addition for Part A:

- To determine the effect of Alhydrogel® adjuvant on the immunogenicity of GBS-NN vaccine.
- To select the dose levels and regimens for vaccination of cohorts in Part B, based on the antibody levels at 8 weeks following the first dose (Day 57).

In addition for Part B:

- To evaluate the immune response to the GBS-NN vaccine up to 1 year following the first dose.

The following endpoints will be evaluated by group and time-point to support these objectives:

- Geometric mean antibody concentration in µg/mL.
- Geometric mean fold increase in antibody concentration.
- Seroconversion rate (proportion of volunteers with fold increase above threshold).

- Proportion of volunteers achieving antibody concentrations above specific thresholds at Day 85 (for Part A these will be 0.5, 1, 2, 4, 8 µg/mL and for Part B these may be modified based on the results from Part A).

The primary immunological endpoints for both Part A and Part B will be the values of these endpoints at Day 85, 12 weeks after the administration of the first dose of vaccine.

7.4 Exploratory Objectives

[redacted]

8. STUDY DESIGN

8.1 Overview

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

The study comprises 2 parts. All cohorts in Part A will incorporate sentinel dosing of 2 volunteers in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further volunteers in that cohort will be dosed until at least 24 hours after dosing the second volunteer, provided that there are no serious or unexplained safety issues as determined by the Investigator.

In Part A, the decision to proceed with administration of the primary dose in subsequent cohorts will be made as follows:

- Safety will be assessed after at least 7 evaluable volunteers in cohort 1 (sentinel and main) have completed Visit 4 (Day 8), at which point the decision will be made whether to proceed with administration of the primary dose in cohorts 2 and 3.
- Safety will be assessed after at least 7 evaluable volunteers in each of cohorts 2 and 3 have completed Visit 4 (Day 8), at which point the decision will be made whether to proceed with administration of the primary dose in both cohorts 4 and 5 or just one of these cohorts.
- Safety will be assessed after at least 7 evaluable volunteers in each of cohorts 4 and 5 have completed Visit 4 (Day 8), at which point the decision will be made whether to proceed with administration of the primary dose in cohort 6.

In Part B, sentinel dosing is not required, and volunteers in all groups may be randomised and dosed concurrently.

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. In Part A, each individual volunteer will be involved in the study for approximately 12 weeks (excluding the 28 day screening period and the 6 month safety follow up phone call). In Part B, each individual volunteer will be involved in the study for approximately 1 year (excluding the 28 day screening period).

9. STUDY POPULATION

9.1 Inclusion Criteria

1. Healthy adult female volunteers (as determined by medical history, physical examination, laboratory test values, vital signs and electrocardiograms [ECGs] at screening) aged 18 – 40 years.
2. Body mass index (BMI) ≥ 18 and ≤ 30 kg/m^2.
3. Volunteers weight ≥ 50kg and ≤100kg at screening.
4. Able to voluntarily provide written informed consent to participate in the study.
5. Must understand the purposes and risks of the study and agree to follow the restrictions and schedule of procedures as defined in the protocol.
6. Volunteers must be pre-menopausal. Volunteers who have had a hysterectomy will have pre-menopausal status confirmed by a FSH and oestradiol test.
7. Females of childbearing potential must have a negative pregnancy test at screening (β HCG) and prior to each dose and must be willing to use an adequate and highly effective method of contraception until at least Day 85 of the study. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, IUDs (Intrauterine Device), condoms, occlusive caps (cervical/vault caps) with spermicidal foam/gel/ film/cream/suppository. True sexual abstinence is acceptable when this is in line with the preferred and usual lifestyle of the volunteer (periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception)
8. In Part A: Volunteers must be non-smokers for at least 3 months prior to first studyvaccine administration. In Part B: Volunteers may be light smokers i.e. up to a maximum of 5 cigarettes per day or nicotine equivalent.
9. Must be willing to consent to have data entered into The Over Volunteering Prevention System (TOPS).
10. The volunteer's primary care physician has confirmed within the last 12 months that there is nothing in their medical history that would preclude their enrolment into a clinical trial.

9.2 Exclusion Criteria

1. Volunteers 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.
2. Pregnant or lactating females.
3. Laboratory values at screening which are deemed to be clinically significant, unless agreed in advance by the Sponsor's Responsible Medic and Principal Investigator.

4. Current or history of drug or alcohol abuse, or a positive urine drugs of abuse test or alcohol breath test at screening or prior to first dosing (note that a positive drugs of abuse result for a regular medication allowed by this protocol will be permitted).
5. Positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
6. Participation in a clinical drug study during the 90 days preceding the initial dose in this study.
7. Any significant illness during the 4 weeks preceding check-in for this study (Day 1).
8. Volunteers with a history of severe allergic reactions after previous vaccination.
9. Volunteers 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.
10. Volunteers receiving immunosuppressive therapy (e.g. systemic steroids, cancer therapies, methotrexate, azathioprine) in the 6 months prior to screening, antibiotics within 10 days of receiving the first dose or taking any short-term medications including over-the-counter preparations, vitamins, herbal and/or mineral supplements 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.
11. Volunteers with tattoos at the proposed site of vaccine administration.
12. Donation of blood or blood products within 90 days prior to vaccine administration.
13. Volunteers who, in the opinion of the Investigator, are unsuitable for participation in the study.

9.3 Planned Sample Size

In Part A, up to 70 healthy female volunteers aged 18 to 40 will be randomised (i.e. up to 7 cohorts of 10 volunteers).

In Part B, up to 240 healthy female volunteers aged 18 to 40 will be randomised (i.e. 3 cohorts of 80 volunteers). The final number of volunteers to be randomised in Part B will be calculated following a review of the data from Part A, and will not exceed 240 volunteers.

At least 7 evaluable volunteers in Part A are required to attend through visit 4 in each cohort in order to provide sufficient data for a decision to dose escalate. If the required number of evaluable volunteers are not obtained in a cohort, then replacement volunteers must be dosed for that cohort, prior to considering dose escalation.

9.4 Allocation of Randomisation Numbers

Each randomised volunteer will be allocated a four digit randomisation number. The randomisation numbers for Part A will be 1001 to 1070, and for Part B will be 2001 to 2240.

In Part A, replacement volunteers will be allocated a randomisation number which is equal to the randomisation number of the volunteer they are replacing plus 100, and they will

receive the same treatment as the volunteer they are replacing, e.g. if randomisation number 1003 is replaced, the replacement volunteer will be allocated the randomisation number 1103.

In Part B, replacement volunteers will be allocated a randomisation number which is equal to the randomisation number of the volunteer they are replacing plus 500, and they will receive the same treatment as the volunteer they are replacing, e.g. if randomisation number 2003 is replaced, the replacement volunteer will be allocated the randomisation number 2503.

9.5 Volunteer Withdrawal

The volunteer has the right to abstain from participation in the study or to withdraw consent to participate at any time without penalty. The Sponsor or the Investigator also holds the responsibility to withdraw a randomised volunteer from the study prematurely if it is considered in the best interest of the volunteer. The entire study may be stopped if there are unpredicted safety concerns.

A volunteer'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 volunteer deviates from the treatment plan specified in the protocol (e.g. failure to attend study visits).
- The volunteer 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 volunteer 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.

9.6 Volunteer Replacement

At least 7 evaluable volunteers in Part A are required to attend through visit 4 in each cohort in order to provide sufficient data for a decision to dose escalate. If the required number of evaluable volunteers are not obtained in a cohort, then replacement volunteers must be dosed for that cohort, prior to considering dose escalation.

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 vaccine will be supplied [redacted]

[redacted]

[redacted]

[redacted]

In Part A, GBS-NN will be administered with and without Alhydrogel® (see table below for anticipated dose regimens). Cohorts in Part B may also receive GBS-NN without Alhydrogel® depending on the dosing regimens chosen. The procedure for the assembly of the different dose levels for Part A of the study is described in detail in the Pharmacy Procedure "Assembly of GBS-NN and placebo doses". This procedure will be followed and, if required, amended to allow the assembly of additional dose strengths if indicated in Part B.

[redacted]

Individual volunteer treatments will be dispensed by the [redacted] pharmacist 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 placebo vaccine [redacted]

It is currently anticipated that the following dosing strategy will be employed, however this may be modified, see below.

Part A:

Three dose levels will be selected, with and without Alhydrogel®: A, B, and C (where A is the lowest dose and C is the highest dose). It is anticipated that these doses will be 10µg, 50µg and 250µg, although these may be modified following ongoing review of data by the Safety Review Committee. The dose increase between cohorts will not exceed a five-fold increase.

It is anticipated that each cohort will receive the following dose regimen as described in the table below.

Note that cohort 7 is an optional cohort, and will proceed if deemed necessary to test an additional dosing regimen at a dose level below 250 μg, which will be determined following an ongoing review of the data.

Cohort	Dose schedule	Dose level	Adjuvant
1	Day 1, 29	10μg (A)	None
2	Day 1, 29	50μg (B)	None
3	Day 1, 29	10μg (A)	Alhydrogel®
4	Day 1, 29	250μg (C)	None
5	Day 1, 29	50μg (B)	Alhydrogel®
6	Day 1, 29	250μg (C)	Alhydrogel®
7	TBD	TBD, not exceeding 250 μg	TBD

Anticipated dose regimens in Part A

The aim of the dose finding overall is to identify the minimum dose level which provides the maximum immune response in terms of seroconversion rate, level of specific IgG reached and shortest time to peak level, whilst maintaining an acceptable safety profile.

It is anticipated that the results from Part A will indicate whether the optimal dose level lies between 10μg and 50μg, or between 50μg and 250μg. The effect of Alhydrogel® on these parameters will guide the decision on whether to include it in one or more cohorts in Part B.

Part B:

The levels of GBS-NN specific IgG observed in Part A at Day 57, along with the safety profile, will be used to define a narrower range of dose levels to explore in Part B, where the group sizes are larger and the significance of any observed differences in immune responses will be measurable.

It is currently anticipated that three dose regimens will be selected for evaluation in Part B. At least two dose levels will be evaluated, which may be the same or different to those administered in Part A, but will not exceed the highest dose administered in Part A. It is anticipated that the regimens in Part B will comprise two doses of Alhydrogel® adjuvanted vaccine with the second being administered after a variable interval, not exceeding four weeks. It is, however, possible that a single dose of vaccine may be evaluated in Part B.

10.2 Randomisation

Volunteers 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.

10.3 IMP Administration

Administration will be by intramuscular injection, preferably into the non-dominant arm. The dominant arm may be used if it is not possible to administer into the non-dominant arm e.g. due to an ongoing injection site reaction, or tattoo.

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

Following database soft lock after visit 10 at 12 weeks for both Part A and Part B, dedicated members of the Data Management and Statistical teams will be unblinded. Study volunteers and clinical staff at the study site will remain blinded until after completion of the final follow-up visit in Week 52.

For the analysis of IgG concentration data up to Day 57 in Part A, to enable dose selection for Part B, a separate statistician will be unblinded to perform the analysis.

10.5 Vacccine 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 GCP guidelines as well as appropriate regulations. Studyvaccines will be stored according to the instructions on the label as received by the manufacturer.

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 volunteers, 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 responsible pharmacist 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 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

Medications which are not permitted prior to study start are detailed in the exclusion criteria.

11.2 Concomitant 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. Paracetamol will be permitted for the treatment of headache or other symptoms.

Any medication the volunteer takes other than study vaccine, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications taken during the study must be recorded in the CRF.

11.3 Other Restrictions

The Investigator or designee will request that volunteers 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 to dosing.
- Use of cosmetics or creams at the site of vaccination within 24 hours prior to dosing.
- 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

12.1 Screening Period (Part A and Part B)

Screening assessments for Part A and Part B 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, tympanic 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 breath test
- Urine drugs of abuse test (methadone, methamphetamine, cannabis, phencyclidine, benzodiazepines, cocaine, opiates, tricyclic antidepressants, barbiturates and amphetamines)
- A review of all medications taken in the previous month

12.2 Treatment Period and Post-Study Period

12.2.1 Part A

Volunteers will receive one of up to 7 dosing regimens of GBS-NN or placebo on 1 or 2 occasions – a primary dose will be administered at Visit 2 and volunteers will remain in the study unit for at least 8 hours post-dose, and if a booster dose is required, this will be administered at Visit 6. There will be a time interval of 4 weeks between Visit 2 and Visit 6, although this time interval may change if the dosing regimen is changed. There will be 10 volunteers in each group, 8 randomised to active and 2 to placebo. All cohorts in Part A will incorporate sentinel dosing of 2 volunteers in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further volunteers in that cohort will be dosed until at least 24 hours after dosing the second volunteer, 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 subsequent cohorts will be made as described in Section 12.5.

The following assessments will be carried out at these visits:

Visit 2

A urine pregnancy test, brief physical examination, urine drugs of abuse test and alcohol breath test will be performed to confirm eligibility. Eligible volunteers will be randomised to receive active or placebo on 1 or 2 occasions (all volunteers will receive a primary dose at Visit 2 and a booster dose of the same medication (active or placebo) will be administered at Visit 6 if required). The dose administered, the number of doses and the time interval between doses will be dependent on the data generated from the preceding cohort and will be decided by the Safety Review Committee. A pharmacodynamic blood sample will be taken to measure pre-existing antibody levels prior to dosing. The primary dose will be administered at Visit 2 and volunteers will remain in the study unit for at least 8 hours post-dose. Vital signs will be recorded pre-dose and at 2 and 6 hours post-dose A brief medical examination (including an assessment of the injection site) will be performed prior to discharge to ensure the volunteer is fit for discharge.

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 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 after administration of the primary dose. This visit will be performed via telephone and a review of AEs and concomitant medications will be performed.

Visit 6

Visit 6 will be performed 4 weeks after Visit 2. A booster dose will or will not be administered at this visit depending on the decision made by the Safety Review Committee for each cohort.

If a booster dose is administered at this visit, the following assessments will be performed: an assessment of the injection site and a pharmacodynamic blood sample will be taken to measure antibody response prior to dosing. A urine pregnancy test will be performed prior to dosing. A booster dose will be administered. Volunteers will remain in the study unit for at least 4 hours post-dose. Vital signs will be recorded pre-dose and at 2 hours post-dose. A brief medical examination (including an assessment of the injection sites) will be performed prior to discharge to ensure the volunteer is fit for discharge.

If a booster dose is not administered at this visit, the following assessments will be performed: an assessment of the injection site and a pharmacodynamic blood sample will be taken to measure antibody response.

AEs and concomitant medications will be reviewed whether a booster dose is administered or not.

Visit 7 (Only if a booster dose is administered)

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. If a booster dose is not administered, this visit will not be performed.

Visit 8

Visit 8 will be performed 2 weeks 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 AEs and concomitant medications will be reviewed.

Visit 9

Visit 9 will be performed 8 weeks 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.

Post-Study Medical (Visit 10)

A post-study medical will be performed 12 weeks 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, 12-lead ECG, urinalysis, blood samples for haematology and biochemistry, serum pregnancy test (if applicable) and a review of AEs and concomitant medications.

Safety Follow-Up (Visit 11)

A safety follow-up phone call will be performed 3 months after the end of the study (Visit 10) i.e. 6 months following the first study vaccine administration to check the general health of the volunteer and to review significant AEs.

[redacted]

In both Part A and Part B, following the primary dose volunteers will remain in the study unit for 8 hours post-dose to ensure that no significant AEs occur and the medicinal product is well tolerated. No additional acute safety concerns are considered likely to occur following 8 hours of observation. Following the booster dose volunteers will remain

in the clinic for at least 4 hours post-dose, as the volunteer has tolerated the initial dose, and therefore, tolerability should be consistent. The concern is for an acute systemic reaction following the booster dose. It is not considered necessary to keep the volunteers in the study unit overnight as no samples are being taken and the time intervals are considered appropriate to assess the safety and tolerability prior to discharge.

12.2.2 Part B

Volunteers will receive one of 3 dosing regimens (X, Y or Z) of GBS-NN or placebo on 1 or 2 occasions – a primary dose will be administered at Visit 2, and if a booster dose is required, this will be administered at Visit 6. There will be up to 80 volunteers in each group, up to 60 randomised to active vaccine and up to 20 to placebo.

The following assessments will be carried out at the visits during the Treatment Period:

Visit 2

A urine pregnancy test, brief physical examination, urine drugs of abuse test and alcohol breath test will be performed to confirm eligibility. Eligible volunteers will be randomised to receive active or placebo on 1 or 2 occasions (all volunteers will receive a primary dose at Visit 2 and a booster dose will be administered at Visit 6 if required). The dose administered and the number of doses will be decided based on the results of Part A. Vaginal and rectal swabs will be taken to assess colonisation by Group B streptococcus (GBS) and a pharmacodynamic blood sample will be taken to measure pre-existing antibody levels prior to dosing.

The primary dose will be administered at Visit 2 and volunteers will remain in the study unit for at least 2 hours post-dose. Vital signs will be recorded pre-dose and at 2 hours post-dose. A brief medical examination (including an assessment of the injection site) will be performed prior to discharge to ensure the volunteer is fit for discharge.

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, and vital signs will be recorded and AEs and concomitant medications will be reviewed.

Visit 4

Visit 4 will be a performed 1 week after administration of the primary dose by telephone to review AEs and concomitant medications.

Visit 5

Visit 5 will be performed 2 weeks after after administration of the primary dose and the following assessments will be performed: an assessment of the injection site, and AEs and concomitant medications will be reviewed, a pharmacodynamic blood sample will be taken to measure antibody response. Vital signs will be recorded, safety blood samples for haematology and biochemistry will be collected and urinalysis will be performed.

Visit 6

Visit 6 will be performed 4 weeks after Visit 2, although this time interval may change depending on the dose regime chosen. A booster dose will or will not be administered at this visit depending on the dose regime chosen.

If a booster dose is administered at this visit, the following assessments will be performed: an assessment of the injection site, vaginal and rectal swabs will be taken to assess colonisation by GBS and a pharmacodynamic blood sample will be taken to measure

antibody response prior to dosing. A urine pregnancy test will be performed prior to dosing. A booster dose will be administered. Volunteers will remain in the study unit for at least 2 hours post-dose. Vital signs will be recorded pre-dose and at 2 hours post-dose. A brief medical examination (including an assessment of the injection sites) will be performed prior to discharge to ensure the volunteer is fit for discharge.

If a booster dose is not administered at this visit, the following assessments will be performed: an assessment of the injection site, vaginal and rectal swabs will be taken to assess colonisation by GBS and a pharmacodynamic blood sample will be taken to measure antibody response.

AEs and concomitant medications will be reviewed whether a booster vaccination is administered or not.

Visit 7 (To be conducted only if a booster dose is administered)

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. If a booster dose is not administered, this visit will not be performed.

Visit 8

Visit 8 will be performed 2 weeks after 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 AEs and concomitant medications will be reviewed.

Visits 9 and 10

These are follow-up visits for the assessment of pharmacodynamic markers and/or safety up to the timing of the primary endpoint (Visit 10 i.e. Week 12).

Visit 9 (week 8) and Visit 10 (week 12, timing of primary endpoint) will take place at the study unit and the following assessments will be performed: vaginal and rectal swabs will be taken to assess colonisation by GBS, a pharmacodynamic blood sample will be taken to measure antibody response, vital signs will be recorded, an assessment of the injection sites will be performed and AEs and concomitant medications will be reviewed. At Visit 10 (week 12) a urine pregnancy test will also be performed.

Visits 11, 12, 13, 14, 15, 16, 17, 18 and 19

Visit 11 (week 16), Visit 13 (week 24), Visit 15 (week 32) and Visit 17 (week 40) will take place at the study unit and the following assessments will be performed: vaginal and rectal swabs will be taken to assess colonisation by GBS, a pharmacodynamic blood sample will be taken to measure antibody response, vital signs will be recorded, an assessment of the injection site will be performed and significant AEs and concomitant medications will be reviewed.

The remaining visits [Visit 12 (week 20), Visit 14 (week 28), Visit 16 (week 36), Visit 18 (week 44) and Visit 19 (week 48)] will be conducted via a phone call and AE's and concomitant medications will be reviewed.

Post-Study Medical (Visit 20)

A post-study medical will be performed 12 months following the first injection and the following assessments will be carried out: an assessment of the injection site, vaginal and rectal swabs will be taken to assess colonisation, a pharmacodynamic blood sample will

be taken to measure antibody response, physical examination, vital signs (heart rate and blood pressure, including tympanic temperature and respiration rate), 12-lead electrocardiogram (ECG), urinalysis, blood samples for haematology and biochemistry, serum pregnancy test (if applicable) and a review of AEs and concomitant medications.

Phenotypic and genetic analyses may be performed on GBS strains isolated from volunteers' vaginal and rectal swabs.

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 volunteer 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:

Haematology

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

Biochemistry

Sodium
Potassium
Chloride
Bicarbonate
Blood urea

Creatinine
Creatine Kinase
Glucose (in a fasting state at screening)
Calcium
Albumin
Cholesterol
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

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

Vital signs will be recorded in the supine position, after the volunteer 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 ≤ 38°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 ±10 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 +/- 1 day.

The time window for Visit 11 in Part A is +/- 1 week.

The time window for visits from Visit 11 in Part B onwards is +/- 3 weeks.

12.5 Safety Monitoring Board and Safety Data Review Meetings (Part A only)

All cohorts in Part A will incorporate sentinel dosing of 2 volunteers in each cohort for the primary dose only: 1 on active treatment and 1 on placebo. No further volunteers in that cohort will be dosed until at least 24 hours after dosing the second volunteer, provided that there are no serious or unexplained safety issues as determined by the Investigator.

In Part A, the decision to proceed with administration of the primary dose in subsequent cohorts will be made as follows:

- Safety will be assessed after at least 7 evaluable volunteers in cohort 1 (sentinel and main) have completed Visit 4 (Day 8), at which point the decision will be made to proceed with administration of the primary dose in cohorts 2 and 3.
- Safety will be assessed after at least 7 evaluable volunteers in each of cohorts 2 and 3 have completed Visit 4 (Day 8), at which point the decision will be made to proceed with administration of the primary dose in both cohorts 4 and 5 or just one of these cohorts.
- Safety will be assessed after at least 7 evaluable volunteers in each of cohorts 4 and 5 have completed Visit 4 (Day 8), at which point the decision will be made to proceed with administration of the primary dose in cohort 6.

The following safety data will be reviewed:

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

The Safety Monitoring Board will include 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 Safety Monitoring Board.

The Safety Monitoring Board 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, including safety data entered on to the electronic CRF

(eCRF) by the site and clinical laboratory test results transferred to the Data Management provider from the safety laboratory.

After review and discussion of all the data, the decision will be made on dose escalation and documented by signature of the Dose Escalation Approval Form by the voting members of the Safety Monitoring Board. 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.

At least 7 evaluable volunteers in Part A are required to complete through visit 4 in each cohort in order to provide sufficient data for a decision to dose escalate. If the required number of evaluable volunteers are not obtained in a cohort, then replacement volunteers must be dosed for that cohort, prior to considering dose escalation. The Safety Monitoring Board may also decide to repeat a dose level or choose an intermediate dose.

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 volunteers will be discontinued from the study if they meet any of the individual volunteer stopping criteria as described in Section 12.6.

In Part B, sentinel dosing is not required, and volunteers in all groups may be randomised and dosed concurrently.

12.6 Individual Volunteer Stopping Criteria

Volunteers who meet one or more of the following stopping criteria will receive no further doses of 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 (>38.9^{o}C and >24 hours) at the Investigator's discretion
- SAE related to the study agent

The medical safety of the volunteer 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 volunteers in a cohort experience a severe site reaction.
- If one of the sentinel group or more than 20% of the volunteers in a cohort experience a severe systemic reaction.
- If one of the sentinel group or more than 20% of the volunteers in a cohort experience a persistent febrile reaction (>38.9^{o}C and >24 hours)
- 1 or more volunteers experience a SAE related to the study agent.

13. PHARMACODYNAMIC ANALYSIS AND EXPLORATORY ASSESSMENTS

13.1 Pharmacodynamic blood sample – antibody response

Each blood sample will be approximately 20 mL in volume, to yield 2 aliquots each comprising approximately 5mL of serum. Five samples will be collected during Part A which represents approximately 100 mL of blood and 11 samples will be collected during Part B which represents approximately 220 mL of blood.

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

13.2 Streptococcus B swab – vaginal and rectal

Vaginal and rectal swabs will be performed during Part B of the study to assess colonisation by Group B streptococcus.

The vaginal swab will be performed of the lower vagina (vaginal introitus), and this will be followed by a separate swab of the rectum (by insertion of the swab through the anal sphincter). The vaginal swab will be performed without a speculum. Swabs will be kept, shipped and analysed separately.

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

13.3 Exploratory Assessments

14. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING

14.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a volunteer 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. ECG, 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 in Part B (i.e. after Visit 10), AEs will be recorded by the volunteer 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:

Definite: 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 volunteer's clinical state and, if necessary, the reaction returns on re-starting the vaccine (re-challenge).

Probable: A reaction that: follows a reasonable temporal sequence from administration of the vaccine, follows a known or expected response pattern to the suspected vaccine and could not be reasonably explained by the known characteristics of the volunteer's clinical state.

Possible: A reaction that: follows a reasonable temporal sequence from administration of the vaccine and that follows a known or expected response pattern to the suspected vaccine but that could readily have been produced by a number of other factors.

Unlikely: A reaction that: follows a reasonable temporal sequence from administration of the vaccine, does not follow a known or expected response pattern of the suspected vaccine and could readily have been produced by a number of other factors.

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.

AEs defined as definite, probable or possible will be reportable. AEs defined as unlikely or unrelated will not be reported. The output from the statistical analysis will be binary, related or not related.

14.3 Recording and Follow up of Adverse Events

Up to Day 85 (Visit 10), the volunteers 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 volunteer 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. In Part B, following Day 85 (Visit 10) AEs will be recorded by the volunteer 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 hospitalisation or prolongation of existing hospitalisation
- 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 hospitalisation 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:

[redacted]

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

- Protocol number
- Volunteer 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.

A 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, ECG values/changes 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 1 year follow up period in Part B it is possible that one or more volunteers may become pregnant. 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 Diamond Pharma Services, and will inform the Sponsor. Diamond Pharma Services 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 volunteer.

In the event of a pregnancy occurring during the course of the study, and with the written consent of the pregnant woman (under a separate consent form), matched serum samples from the mother and cord blood will be collected and relevant serum analyses will be performed at the University of Lund as described under the exploratory assessments.

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 Eurofins Optimed using SAS statistical software.

15.1 Statistical method description

15.1.1 General information

Statistical results will be separately presented for parts A and B.

Demographic, baseline characteristics and data recorded during the study will be summarised using descriptive statistics by treatment (placebo, vaccine taken alone or vaccine combined with adjuvant) and dose group, unless otherwise specified. If relevant additional descriptive graphs can be provided.

Individual data for all included volunteers 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 for the two study parts

Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum. Descriptive statistics for qualitative parameters will be provided using absolute frequencies (n) and relative frequencies (%).

15.1.3 Inferential statistics

Adequate statistical tests will be used to carry out comparison between treatment/dose groups performed on primary, secondary or exploratory endpoints, even though it is accepted that the power of these tests for groups in Part A will be low due to small numbers of volunteers.

For categorical endpoints, such as local and systemic reactogenicity, a comparison of events intensity (scores) between vaccine dose groups will 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 vaccine dosing regimens, appropriate statistical method (for example: ANOVA) will be used to compare pre-vaccination and post-vaccination levels.

15.2 Studied populations for each study part

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

- **Intention to Treat Set (ITT)**: All included volunteers who receive at least one dose of the study vaccine will be taken into account in the description of the population (disposition, demographic or baseline characteristics);
- **Immunogenicity Set (IG)**: The subset of volunteers who will receive at least one dose of the study vaccine with available pre- and post-vaccination titers.
- **Per Protocol Set (PP)**: All volunteers who receive both doses of the study vaccine and provide evaluable samples for analysis of the primary immunological endpoint and do not violate the protocol.

The Primary and Secondary Safety analyses will be performed on the ITT set. The Secondary Immunological analyses will be performed on the IG set. The “primary” immunological analysis (i.e. the results on Day 85 in both study parts) will also be performed on the PP 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 70 healthy female volunteers will be included in part A (7 cohorts of 10 volunteers) and up to 240 in part B (3 cohorts of 80 volunteers). The final number of volunteers to be randomized in part B will be calculated following a data review from part A.

15.4 Studied criteria for the two study parts

15.4.1 Characteristics of included volunteers

- **Volunteer demographic characteristics**
  For demography, continuous variables (for example: age, height, weight, BMI) and qualitative variables (for example: ethnical origin) will be summarised using descriptive statistics on all included volunteers. Demographic characteristics will be also presented for other study populations (IG and/or PP) if they are different from ITT.

- **Medical history events**

Medical and surgical history events will summarised by System Organ Class (SOC) and Preferred Term (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 volunteer.

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

- **Pregnancy test**
  If applicable, serum pregnancy test will be performed at screening and post-study medical visit and urine pregnancy test will be performed prior each administered dose (primary and booster doses at V2 and V6 respectively) and only for part B at V10. If no booster dose is administered then no pregnancy test will be scheduled at V6. A listing of positive results will be presented by treatment/dose group, volunteer and visit.

- **Previous medications**
  [redacted] a listing will be presented by treatment/dose group and volunteer.

- **Concomitant medication**
  [redacted] olunteers who received concomitant treatments along with the study conduct (including emergent and non-emergent treatments) will be listed by treatment/dose group.

  If relevant, frequency of volunteers taking concomitant medications and occurrence number of each medication will be summarised by Anatomic and Therapeutic Class (ATC) and Preferred Term (PT) for each treatment/dose group.

15.4.2 Primary endpoint for the two study parts

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

All the included volunteers (including the withdrawal and dropout volunteers) will be evaluated for safety analysis (ITT).

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). 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: definite / probable / possible / unlikely / 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 volunteers with at least one TEAE (based on ITT). In case of few TEAEs (≤ 5 per study part for example), only a listing will be performed.

Vaccine related TEAEs (*i.e.* definite, probable or possible relationship to study vaccine) will be summarised by MedDRA codes (SOC and PT) and treatment/dose group. In case of few vaccine related TEAEs (≤ 5 per study part for example), only a listing will be performed. TEAEs not related to study vaccine (i.e. unlikely or unrelated relationship to study vaccine) will also be summarized by MedDRA codes.

Two distinct listings of TEAEs and NTEAEs will be presented by treatment/dose group, volunteer and MedDRA codes in order to provide more information about adverse events (example: description, duration, time since last administration if applicable, seriousness, any actions taken as concomitant medication or hospitalization).

- **Laboratory tests**

  Biochemistry and haematology tests will be performed at V1 (screening), V4 (part A), V5 (part B), V8 (parts A and B) and post-study medical visit (V10 for part A and V20 for part B).

  Parameter values, position according to laboratory ranges (if available) and investigator assessment will be described according to visit for each treatment/dose group. In order to study evolution of parameters after vaccination, parameter values changes from pre- to post-dose visits will be performed. Emergent values (for parameters with available laboratory ranges) with their corresponding position according to ranges will be listed by treatment/dose group and volunteer.

- **Urinalysis**

  Urinalysis will be performed at V1 (screening), V4 (part A), V5 (part B), V8 (parts A and B) and post-study medical visit (V10 for part A and V20 for part B).

  Parameter values (quantitative or binary results, *i.e.* positive/negative), position according to laboratory ranges (if available) and investigator assessment will be described according to visit for each treatment/dose group. In order to 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 volunteer.

- **Vital signs**

  Vitals signs will be characterised by heart rate, blood pressure, tympanic temperature and respiratory rate. Vital signs will be assessed at V1 (screening), V2 (pre-dose, T2h and T3h post-dose), V3, V4 (part A only), V6 (pre-dose and T2h post-dose for volunteers receiving booster dose), V7 (only if administered booster dose), V8, and post-study medical visit (V10 for part A and V20 for part B). For study part B, additional vital signs assessments will be performed at V5, V8, V9, V10, V11, V13, V15 and V17.

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 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) with their corresponding position according to reference ranges will be listed by treatment/dose group and volunteer.

- **12-lead ECG parameters**

  ECG will be assessed at V1 (screening) and post-study medical visit (V10 for part A and V20 for part B).

  Parameter values, position according to reference ranges and investigator assessment (if available) will be described according to visit for each treatment/dose group. In order to study evolution of parameters after vaccination, parameter values changes from screening to post-study medical visit will be performed. Emergent values (for parameters with available reference ranges) with their corresponding position according to reference ranges will be listed by treatment/dose group and volunteer.

- **Physical examination**

  Abnormal physical examinations recorded at post-study medical visit (V10 for part A and V20 for part B) will be listed according to treatment/dose group and volunteer.

15.4.3 Secondary Safety Endpoints

The safety secondary objective for part B is to evaluate the long term safety profile of the GBS-NN vaccine up to 1 year following the first dose.

The same endpoints will be evaluated as for the primary objective.

15.4.4 Secondary Immunological Endpoints

The secondary immunological objectives for both parts of the study are:

- To evaluate IgG antibody responses induced by different vaccine doses alone or in the presence of Alhydrogel over time in healthy female volunteers:
- To determine the impact of pre-existing antibody levels on the vaccine-induced antibody response:

In addition for Part A:
- To determine the effect of Alhydrogel® adjuvant on the immunogenicity of GBS-NN vaccine
- To select the dose levels and regimens for vaccination of cohorts in Part B, based on the antibody levels at 8 weeks following the first dose (Day 57)

In addition for Part B:

- To evaluate the immune response to the GBS-NN vaccine up to 1 year following the first dose

Immunological parameters measured to evaluate objectives

In order to evaluate these objectives, GBS-NN 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 volunteer:

- Antibody concentration at each sample point (µg/mL)
- Fold increase over pre-immunisation level (Day 1) in antibody concentration 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 concentration (with 95% c.i.)
- Geometric mean fold increase in antibody concentration (with 95% c.i.)
- Seroconversion rate at each sample point (proportion of volunteers with fold increase above threshold (*see below)
- At the primary immunological endpoint (Day 85) all groups in Part A will be analysed according to the proportion of volunteers whose specific antibody level (µg/mL) exceeds the following thresholds: 0.5; 1.0; 2.0; 4.0; 8.0 µg/mL. The analysis will be repeated for Part B, where the threshold values may be adjusted based on the results of Part A.

* For Part A the threshold to define a positive response will be set arbitrarily to 2.5-fold rise above base-line, as is common practice in FIM vaccine studies. For Part B, the threshold will be set based upon the data derived from Part A. The fold increase for all 12 placebo recipients at Days 29, 43, 57 & 85 will be considered. The mean and standard deviation will be calculated and the cut-off defined as two standard deviations above the mean.

The primary immunological endpoints (still secondary study endpoint) for both Part A and Part B will be the values of these endpoints at Day 85, 12 weeks after the administration of the first dose of vaccine).

In Part A, the immunological endpoints at Days 1, 29 and 57 will be reported separately by group in a blinded fashion to enable the dose selection for Part B

Additional analyses to address objectives

For each group the individual data will be presented as scatter plots and cumulative frequency distributions at each time-point

Correlation plots will be generated to compare the specific antibody concentrations before vaccination and at 12 weeks after the first dose to evaluate the influence of pre-existing antibody levels on responses.

Statistical significance of differences in endpoint values

Statistical tests will be carried out to compare results between treatment groups, depending on studied variable type (see section inferential statistics). These analyses will be fully detailed in the SAP. In brief the following comparisons between groups will be made at Day 29 and Day 84 (and at Day 57 in Part A only):

Part A:

- Placebo group (total 12 volunteers, 6 with buffer only and 6 with alhydrogel) against all other dose groups
- Each dose level with and without Alhydrogel®
- 10µg vs 50µg, 10µg vs 250µg, 50µg vs 250µg in volunteers vaccinated with GBS-NN alone
- 10µg vs 50µg, 10µg vs 250µg, 50µg vs 250µg in volunteers vaccinated with GBS-NN in the presence of Alhydrogel
- For all groups and parameters Day 29 vs Day 85

Part B:

- Placebo group against all other dose groups (regimens to be decided)
- Group A vs Group B; Group A vs Group C; Group B vs GroupC
- For all groups and parameters Day 29 vs Day 85

15.4.5 Exploratory endpoints

Exploratory Objectives

[redacted]

[redacted]

16. ETHICS AND REGULATORY

16.1 Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and 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, volunteer information sheet (VIS), informed consent form (ICF) and any study related information or documents issued to volunteers will be reviewed and approved along with other required documents by the Ethics Committee (EC) and each study site's local EC before volunteers 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 volunteer in the study. The Sponsor will always also provide the EC/CA with a summary of the study's outcome.

16.3 Volunteer Information and Informed Consent

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

Prior to study start, the volunteers 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 volunteer 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 volunteer should understand the VIS and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each volunteer will be given a copy of the signed informed consent and written information.

The original signed ICF for each volunteer 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 Data Protection Act (1998) 95/46/EC. 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. 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 volunteer 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 volunteer's source data records. SDV will be performed with due regard for volunteer 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 volunteer 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 volunteer 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 volunteer 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

Part A 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[a]	Day 29[b]	Day 30[b,c]	Day 43[b]	Day 57[b]	Day 85	Day 183[a]
Informed Consent	X										
Inclusion/ Exclusion Criteria	X										
Demography	X										
Medical History	X										
Physical Examination[d]	X	X								X	
Height, Weight, BMI	X										
Vital signs[e]	X	X[f]	X	X		X[g,h]	X	X		X	
12-lead ECG	X									X	
Urinalysis	X			X				X		X	
Safety laboratory tests	X			X				X		X	
HIV, Hep B and Hep C	X										
Pregnancy test[i]	X	X				X[h]				X	
Alcohol breath test	X	X									
Urine drugs of abuse test	X	X									
Review of volunteer eligibility		X									
Randomisation		X									
Administration of primary dose[j]		X									
Administration of booster dose						X[h]					
PD blood sample – antibody response		X				X		X	X	X	
Brief medical examination[k]		X				X					
Assessment of injection site(s)[l]			X	X		X[m]	X	X	X	X	
AE check		X								X	X
Con med check	X	X								X	

Footnotes

a. Visit performed by telephone.
b. Day numbers of Visits 6, 7, 8 and 9 may change if the dosing regimen is changed.
c. Visit 7 not required if booster dose not administered.
d. Full physical examination at screening and post-study medical. Brief physical examination prior to first dose.
e. Heart rate, blood pressure, tympanic temperature and respiration rate.
f. Vital signs at Visit 2 will be recorded pre-dose and at 2 and 6 hours post-dose.
g. Vital signs at Visit 6 will be recorded pre-dose and at 2 hours post-dose.
h. Administration of booster dose only if applicable to this cohort. If booster dose not administered, vital signs and pregnancy test are not to be performed.
i. Serum pregnancy test at screening and post-study medical. Urine pregnancy test prior to each dose.
j. Sentinel dosing for all cohorts for the primary dose only.
k. Brief medical examination (including assessment of the injection site(s) to determine eligibility for discharge at least 8 hours post-dose on Day 1 and at least 4 hours post-dose on Day 29.
l. Photographs may be taken of injection site reactions as required.
m. Assessment of first injection site, to be assessed pre-dose.

Part A Schedule of Assessments – Exploratory Assessments

	Treatment Period				Post-Study Medical
	Visit 2	**Visit 6**	**Visit 8**	**Visit 9**	**Visit 10**
Assessment	Day 1	Day 29	Day 43	Day 57	Day 85
Ig ELISA	C1-C6	C1-C6	C1-C6	C1-C6	C1-C6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]
[redacted]	[redacted]				[redacted]
[redacted]	[redacted]				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(C = cohort)

Part B Schedule of Assessments

	Screening Period	Treatment Period																		Post-Study Medical
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4[a]**	**Visit 5**	**Visit 6**	**Visit 7[b]**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12[a]**	**Visit 13**	**Visit 14[a]**	**Visit 15**	**Visit 16[a]**	**Visit 17**	**Visit 18[a]**	**Visit 19[a]**	**Visit 20**
	Day -28 to Day -1	Day 1	Day 2	Day 8	Day 15	Day 29	Day 30	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365
Assessment				Week 1	Week 2	Week 4		Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Informed Consent	X																			
Inclusion/ Exclusion Criteria	X																			
Demography	X																			
Medical History	X																			
Physical Examination[c]	X	X																		X
Height, Weight, BMI	X																			
Vital signs[d]	X	X[e]	X		X	X[f g]	X	X	X	X	X		X		X		X			X
12-lead ECG	X																			X
Urinalysis	X				X			X												X
Safety laboratory tests	X				X			X												X
HIV, Hep B and Hep C	X																			
Pregnancy test[h]	X	X				X[g]				X										X
Alcohol breath test	X	X																		
Urine drugs of abuse test	X	X																		
Review of volunteer eligibility		X																		
Randomisation		X																		
Administration of primary dose		X																		
Administration of booster dose						X[g]														
Streptococcus B swab – vaginal		X				X			X	X	X		X		X		X			X
Streptococcus B swab – rectal		X				X			X	X	X		X		X		X			X
PD blood sample – antibody response		X			X	X		X	X	X	X		X		X		X			X
Brief medical examination[i]		X				X														
Assessment of injection site(s)[j]			X		X	X[k]	X	X	X	X	X		X		X		X			X
AE check		X									X									X
Con med check	X	X									X									X

Footnotes

a. Visits 4, 12, 14, 16, 18 and 19 conducted by telephone.

b. Visit 7 not required if booster dose not administered.

c. Full physical examination at screening and post-study medical. Brief physical examination prior to first dose.

d. Heart rate, blood pressure, tympanic temperature and respiration rate.
e. Vital signs at Visit 2 will be recorded pre-dose and at 2 hours post-dose.
f. Vital signs at Visit 6 will be recorded pre-dose and at 2 hours post-dose.
g. Administration of booster dose only if applicable to this cohort, If booster dose not administered, vital signs, and pregnancy test are not to be performed.
h. Serum pregnancy test at screening and post-study medical. Urine pregnancy test prior to each dose and at Visit 10.
i. Brief medical examination (including assessment of the injection site(s)) to determine eligibility for discharge at least 2hours post-dose on Day 1 and at least 2 hours post-dose on Day 29.
j. Photographs may be taken of injection site reactions as required.
k. Assessment of first injection site, to be assessed pre-dose.

Part B Schedule of Assessments – Exploratory Assessments

	Treatment Period								Post-Study Medical
	Visit 2	**Visit 5**	**Visit 6**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 13**	**Visit 20**
	Day 1	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 169	Day 365
Assessment		Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 24	Week 52
Ig ELISA	C1 or C2	C1 or C2	C1 or C2		C1 or C2	C1 or C2		C1 or C2	C1 or C2
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
[redacted]			[redacted]		[redacted]	[redacted]			[redacted]
[redacted]					[redacted]	[redacted]			[redacted]
[redacted]					[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]

(C = cohort)

Note: Cohort 1 or 2 to be selected based on results from Part A. Timepoints for sample collection may be altered based on results from Part A.
a) Time point not entirely fixed and dependent on results obtained in Part A.

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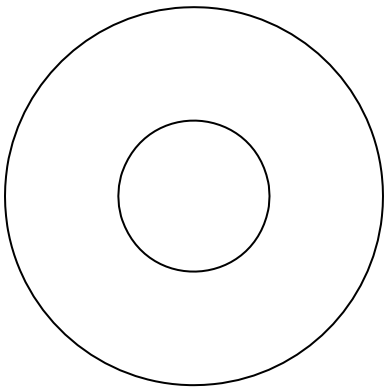
APPENDIX 1

INJECTION SITE TOLERABILITY ASSESSMENT

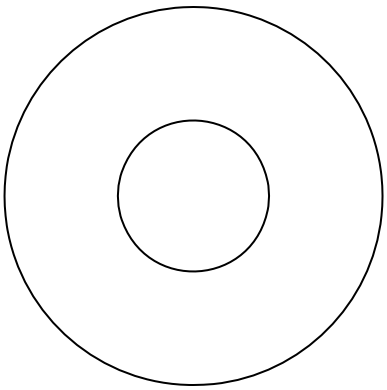
Tolerability assessments will be performed by a member of the clinical staff. An additional assessment by a physician will be made in the event of a local reaction being evaluated as moderate or severe. All measurements (in cm) refer to the longest dimension.

Redness



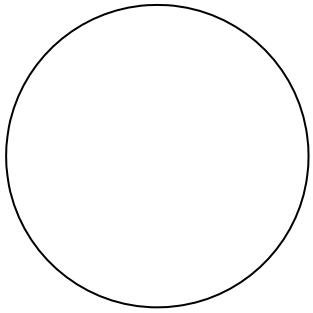
Grade	Description:	
0	NONE	No visible redness
1	MILD	Greater than 0 to 2 cm (incl.) redness
2	MODERATE	Greater than 2 to 5 cm (incl.) redness
3	SEVERE	Greater than 5 cm redness

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

Volunteers 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