TITLE PAGE

Protocol Title:

A randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of three doses of Group B Streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in elderly participants aged 55 to 75.

Protocol Number: MVX0006

Amendment Number: Not Applicable

Compound: Group B Streptococcus Vaccine (GBS-NN/NN2)

Brief Title:

Study to evaluate the safety, tolerability and immunogenicity of three doses of Group B Streptococcus vaccine in elderly participants

Study Phase: I

Sponsor Name: MinervaX ApS

Legal Registered Address: MinervaX ApS, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark

Regulatory Agency Identifier Number(s): EudraCT number: 2022-003681-20

Date of Original Protocol: 09 December 2022

Date of Protocol Amendment 2.0: 03 May 2023

Sponsor Signatory

MinervaX (the Sponsor) approves the contents of this protocol and agrees that it will arrange for the supply of the investigational products described in the protocol and undertakes to report adverse events to the relevant authorities in compliance with the regulations. It further agrees to inform the Investigators of any information that would place the participants at risk by their continuing participation in the trial.

DocuSigned by [redacted]

[redacted] I approve this document
11-May-2023 | 2:48:23 PM BST

11-May-2023

[redacted] F34A3C883463AB44FB4D67

Date

Sponsor's Responsible Physician, MinervaX

DocuSigned by [redacted]

[redacted] Jeg godkender dette dokument
11-May-2023 | 4:54:45 AM PDT

11-maj-2023

[redacted] BDD

Date

Senior Clinical Project Manager

Principal Investigator Signatory

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made, if necessary, to protect the safety, rights or welfare of the participants.

[redacted]

Date

Principal Investigator

Medical Monitor name and contact information will be provided separately.

PROTOCOL AMENDMENT 2.0 (03 MAY 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment serves to clarify inconsistencies and to provide further guidance for trial assessments and procedures per clinical study protocol.

Section # and Name (page #)	**Current Language**	**Proposed Language** (New text will be **bolded** and deleted text will be ~~struck through~~)	**Rationale for Change**
1.1 Synopsis (p.17)	Sixty (60) healthy older adult participants aged 55 to 75 years will be randomized in two cohorts; 30 obese and/or diabetic participants aged 55 to 75 years will be randomized in two cohorts.	Sixty (60) healthy older adult participants aged 55 to 75 years **at screening** will be randomized in two cohorts; 30 obese and/or diabetic participants aged 55 to 75 years **at screening** will be randomized in two cohorts.	Clarification that eligible age is considered at screening.
1.3 Schedule of Activities (p.21)	[i] Between Day 57 (28 days post second injection) to Day 168 and from 28 days after the third vaccine to Day 365 only MAAEs, AESIs and SAEs will be collected.	**[i] Solicited AE/SAEs will be collected 7 days post each vaccination in the eDiary.** [j] Between Day ~~57~~**58** (28 days post ~~second~~ **2nd** injection) to Day ~~168~~**161** and from 28 days after the ~~third~~**3rd** vaccine to Day 365 only MAAEs, AESIs**,** and SAEs will be collected. **[k] Between Day 1 to Day 57 and Day 162 to Day 197 all CMs will be collected. Between Day 58 to Day 161 and Day 198 to Visit 12 (Day 365): only CMs taken for MAAEs, AESIs, and SAEs, which are collected within this period will be recorded.**	Table flow chart and table footnotes edited to provide clarity to collection of adverse events (AEs) and concomitant medications (CMs).
5.0 Study Population (p.30)	N/A	**Data from screening procedures will be used for treatment allocation if a procedure is not planned or repeated at Visit 2. Procedures will not be repeated at Visit 4 and Visit 8.**	Clarification how eligibility data should be handled if procedure is not repeated prior to 1st dosing.

Section # and Name (page #)	Current Language	Proposed Language (New text will be **bolded** and deleted text will be ~~struck through~~)	Rationale for Change
5.0 Study Population (p.30)	N/A	• **The investigator should consider whether a participant with BMI ≥18 to <30 kg/m^2 and with prediabetes is eligible for Cohort 1 or 2. This decision can be made based on the CDC definition of prediabetes of an HbA1c of 5.7% to 6.4%.** • **If a participant has a BMI ≥30 to ≤45 kg/m^2 and the participant has prediabetes, the participant would be eligible for Cohorts 3 and 4 as a participant who is obese.** • **For a participant to be included in the Cohorts 3 and 4 as a participant with diabetes (as opposed to a participant who is obese), a pre-existing diagnosis of diabetes, documented by the general practitioner or other treating physician, is required.** • **If the participant is diagnosed with type 2 diabetes, the participant must be on treatment for type 2 diabetes; e.g. metformin, sulphonylureas, or glitazones. The diabetic participant is not eligible for Cohort 3 and 4 if not receiving treatment for type 2 diabetes at study enrolment.**	Clarification on prediabetic conditions regarding eligibility for Cohorts 1 and 2 and clarification of the requirements for a participant to be considered diabetic for assessing allocation to cohorts.

Section # and Name (page #)	**Current Language**	**Proposed Language** (New text will be **bolded** and deleted text will be ~~struck through~~)	**Rationale for Change**
5.1 Inclusion Criteria (p.30)	Participant aged 55 to 75 years.	Participant aged 55 to 75 years of age **at screening.**	Clarification that eligible age is considered at screening.
5.1 Inclusion Criteria (p.30)	Body mass index (BMI) ≥18 and ≤30 kg/m^2 for healthy participants, ≥ 30 to ≤45 kg/m^2 for obese participants and ≥18 to ≤45 kg/m^2 for type 2 diabetic participants.	Body mass index (BMI) ≥18 and ~~≤~~**<**30 kg/m^2 for healthy participants, ≥ 30 to ≤45 kg/m^2 for obese participants and ≥18 to ≤45 kg/m^2 for type 2 diabetic participants **at screening**.	Inconsistency correction, it was unclear which group a participant with a BMI of 30 should be enrolled in.
5.2 Exclusion Criteria (p.31)	NOTE: Patients with type 2 diabetes are to be recruited for Cohort 3 and Cohort 4.	NOTE: Patients with type 2 diabetes are to be recruited for Cohort 3 and Cohort 4. **The autoimmune skin diseases, mild psoriasis and vitiligo, will not be considered as relevant for exclusion. Other autoimmune diseases that are not stable or are progressive/worsening (as evaluated by the investigator) should lead to exclusion.**	While mild psoriasis and vitiligo are considered as autoimmune diseases, they are not considered as relevant for eligibility assessment of a participant. No additional risks for participants with mild psoriasis or vitiligo are expected.
5.2 Exclusion Criteria (p.31)	Participants who have received any vaccine within 30 days of first IMP administration, or who are planning to receive any vaccine (eg, travel vaccines) up to 30 days after each vaccination.	Participants who have received any vaccine within 30 days of ~~first~~ **1st** IMP administration, or who are planning to receive any vaccine (eg, travel vaccines) up to 30 days after each vaccination **and/or 7 days prior to 3rd administration**.	Clarification on time window for participants receiving other vaccines planned around the 3rd study dosing.
6.3.1 Participant Identification (p.34)	Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to the study site.	Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to the study site. **Re-screening of participants will require the allocation of a new participant identification number.**	Clarification regarding re-screened participants.
6.3.2 Treatment allocation to the	Allocation of the participant to treatment within a cohort	Allocation of the participant to treatment within a cohort at	Clarification to ensure consistency with actual

Section # and Name (page #)	Current Language	Proposed Language (New text will be **bolded** and deleted text will be ~~struck through~~)	Rationale for Change
participant (p.34)	at the study site will be performed using a randomisation schedule at the site after confirming eligibility and prior to first dosing.	the study site will be performed using a randomisation ~~schedule~~ **module of the electronic case report form (eCRF) used as Interactive Response System (IRS)** at the site after confirming eligibility and prior to ~~first~~ **1st** dosing.	setup of the randomisation system used.
6.6 Concomitant Therapy (p.36)	Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with… Concomitant medications (CM) may be recorded on the electronic diary (eDiary) of the participant.	Any medication or vaccine (including OTC or prescription medicines~~, recreational drugs, vitamins, and/or herbal supplements~~) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with… Concomitant medications (CM) ~~may~~ **will** be recorded ~~on~~ **in** the electronic diary (eDiary) of the participant **7 days after each vaccination**. ***NOTE: The overall collection of CMs during the study period should be done as follows (see Section 8.3.1 for AE collection details):*** • ***Day 1 – Visit 6 (Day 57): All CMs associated with an AE.*** • ***Day 58 – Day 161: Only CMs taken for MAAEs, AESIs, and SAEs, which are collected within this period.*** • ***Day 162 (7 days prior to 3rd vaccination at Visit 8) – Visit 10 (Day 197): All CMs associated with an AE.*** • ***Day 198 – Visit 12 (Day 365): Only CMs***	Information regarding the use of recreational drugs, vitamins, and/or herbal supplements would not be required to support medical overview on participant safety nor increase the scientific value of the trial. Therefore, it is unnecessary to collect information on the use of recreational drugs, vitamins, and/or herbal supplements. Furthermore, the clarification was added that concomitant medication between 28 days post dose 2nd investigational medicinal product (IMP) administration until 3rd study IMP administration will not be required except for MAAEs, AESIs, and SAEs. The collection of unrelated concomitant medication during this period does not increase the scientific value of the study and will therefore be limited.

Section # and Name (page #)	Current Language	Proposed Language (New text will be **bolded** and deleted text will be ~~struck through~~)	Rationale for Change
		taken for MAAEs, AESIs, and SAEs collected within this period.	
6.6.1 Permitted Concomitant Medication (p.37)	Non steroidal anti-inflammatory drugs or paracetamol at doses of ≤4 g/day, will be permitted for use any time during the study for the treatment of headache or other symptoms.	Non-steroidal anti-inflammatory drugs or paracetamol at doses of ≤4 g/day, will be permitted for use any time during the study**, except within 72 hours before each vaccination,** for the treatment of headache or other symptoms.	Clarification to ensure consistency with exclusion criteria.
6.6.2 Prohibited Concomitant Medications (p.37)	Any short-term medications including OTC preparations, with the exception of non-steroidal anti-inflammatory drugs or paracetamol.	~~Any short-term medications including OTC preparations, with the exception of non-steroidal anti-inflammatory drugs or paracetamol.~~	Text deleted to avoid confusion. The exclusion criteria provide sufficient clarity regarding prohibited medication.
6.6.2 Prohibited Concomitant Medications (p.37)	Vaccines within 30 days of first IMP administration or planning to receive any vaccine up to 30 days after each study vaccination, with the exception of emergency vaccinations or vaccination campaigns, which will be permitted not less than 7 days before and after study vaccination.	Vaccines within 30 days of ~~first~~ **1st** IMP administration ~~or planning to receive any vaccine~~ **and** up to 30 days after each study vaccination **and 7 days prior to 3rd IMP administration,** with the with the exception of emergency vaccinations or vaccination campaigns, which will be permitted not less than 7 days before and after study vaccination.	Clarification of prohibited use of vaccines, has been edited to specify that vaccines are prohibited within 30 days of 1st IMP administration and up to 30 days after each study vaccination and 7 days prior to 3rd IMP administration.
8.2.4 Electronic Diary (p.43)	For solicited systemic reactions (nausea, vomiting, diarrhoea, headache, fatigue, myalgia)	For solicited systemic reactions (**chills, muscle pains/myalgia, malaise,** nausea, vomiting, ~~diarrhoea,~~ headache, **and** fatigue~~, myalgia~~)	Correction of inconsistency that was present in the protocol.
8.3.1 Time Period and Frequency for Collecting AE and SAE Information (p.43)	N/A	***NOTE: The overall collection of AEs during the study period should be done as follows:*** • ***Day 1 – Visit 6 (Day 57): All AEs***	Clarification regarding overall collection of AEs added.

Section # and Name (page #)	Current Language	Proposed Language (New text will be **bolded** and deleted text will be ~~struck through~~)	Rationale for Change
		• ***Day 58 – Day 161: Only MAAEs, AESIs, and SAEs*** • ***Day 162 – Visit 10 (Day 197): All AEs*** • ***Day 198 – Visit 12 (Day 365): Only MAAEs, AESIs, and SAEs***	
10.2 Appendix 2, Clinical Laboratory Tests, Table 6 (p.57)	White blood cell count with differential	White blood cell count with differential **white blood cell (Absolute and percentages):**	Clarification of white blood cell parameter
10.2 Appendix 2, Clinical Laboratory Tests, Table 6 (p.57)	Globulin	Globulin **(Calculated by: total protein – albumin)**	Clarification regarding how the result of the serum globulin will be obtained.
10.2 Appendix 2, Table 6: Clinical Laboratory Tests (p.57)	Human immunodeficiency virus (HIV) I and II	Human immunodeficiency virus (HIV) ~~I and II~~	Local lab is not able to distinguish human immunodeficiency virus (HIV) I versus HIV II, therefore, this detail was removed.
10.3 Appendix 3: AEs and SAEs (p.59)	Definition of Unsolicited and Solicited AE An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.	**Timing for the collection of AEs, ~~D~~definition** of Unsolicited and Solicited AE ~~An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.~~ • **All AEs, AESIs, and SAEs will be collected from the 1st IMP administration.** • **Solicited AEs are predefined events/symptoms that the participant is**	Correction made regarding timing for the collection of AEs as well as clarification of what is considered an unsolicited AE and what is considered a solicited AE.

Section # and Name (page #)	Current Language	Proposed Language (New text will be **bolded** and deleted text will be ~~struck through~~)	Rationale for Change
		specifically asked to record in the eDiary. The predefined solicited AEs include: Injection site reactions (redness, swelling, pain, tenderness, and itching) and systemic reactions (pyrexia, chills, muscle pains/myalgia, malaise, nausea, vomiting, headache, and fatigue). • **An AE reported in response to an open question e.g., "Did you experience any other signs/symptoms?", is an unsolicited AE.** • **An unsolicited AE is an AE reported spontaneously by the participant.**	

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of three doses of Group B Streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in elderly participants aged 55 to 75.

Rationale:

The purpose of this Phase 1 trial is to study the safety and immunogenicity of two dose levels, in an older adult population, with and without underlying medical conditions, to assess whether the GBS-NN/NN2 vaccine could potentially be effective in an older adult population and warrant further development in this population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• The primary objective is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine for 4 weeks after each dose of vaccine.	• Safety and tolerability as determined by the occurrence of AEs consisting of local and systemic reactogenicity within 7 days after vaccination (Days 1 through 8 post each dose of the IMP) • Unsolicited AEs, including AESIs, MAAEs and SAEs within 28 days after each vaccination • AESIs, MAAEs, ARs/SARs leading to withdrawal from the study.
Secondary Immunological	
• To evaluate IgG antibody response to the GBS-NN/NN2 vaccine at Day 197 (principal immunological endpoint). • To evaluate IgG antibody responses induced by the three vaccine doses, on a 0-, 1- and 6-month regimen, in older adult participants 4 weeks after each vaccination. • To assess whether pre-existing antibody levels affect the vaccine-induced antibody response. • To evaluate the immune response up to 6 months following the 3rd dose; to be reported in an addendum to the main CSR.	• Geometric mean antibody concentration in µg/mL for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC). • Geometric mean fold increase in antibody concentration for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC). • Seroconversion rate (proportion of participants with a 4-fold increase above baseline – pre dose concentration) at any time post vaccination. • Proportion of participants achieving antibody concentrations for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC) above specific thresholds at Days 29, 57, 169,

Objectives	Endpoints
	and 197 (these thresholds will be 1, 2, 4, and 8 µg/mL).
Secondary Safety	
• To evaluate the long-term safety profile of the GBS-NN/NN2 vaccine between Day 57 (28 days post second injection) to Day 168 and 6 months following the 3rd dose (safety endpoint); to be reported in an addendum to the main CSR.	• Proportion of participants with any SAE from between Day 57 (28 days post second injection) to Day 168 and 28 days after 3rd vaccination (Day 197) up to Day 365. • Proportion of participants with MAAEs, AESIs, ARs/SARs requiring a medical consultation, and or leading to withdrawal from the study from 28 days after 3rd vaccination (Day 197) up to Day 365.
Exploratory	
• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]

AEs = adverse events; AESIs = adverse events of special interest; Alps = alpha-like proteins; ARs = adverse reactions; [redacted]; CSR = clinical study report; [redacted]; GBS = Group B Streptococcus; IMP = investigational medicinal product; [redacted] IgG = Immunoglobulin G; MAAEs = medically attended adverse events; [redacted]; SAE = serious adverse event; SAR = serious adverse reaction.

Overall Design:

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

Eligible participants will be randomised pre dose on Day 1, once all eligibility criteria have been verified. There will be two cohorts comprising 30 healthy older adult participants each and two cohorts comprising 15 obese and/or diabetic older adult participants each (see Figure 1):

- Cohort 1 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (investigational medicinal product [IMP]: placebo).
- Cohort 2 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).
- Cohort 3 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).
- Cohort 4 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).

Number of Participants:

Approximately 90 participants will be randomised in four cohorts.

Cohort Groups and Duration:

Participants will be involved in the study for approximately one year including screening and safety follow-up. The start of the study is defined as Day 1 when participants are randomised. Eligible participants will be administered a dose of GBS-NN/NN2 or placebo on three occasions: the 1st dose will be administered on Day 1, followed by the 2nd and 3rd doses 4 and 24 weeks later, respectively.

Sixty (60) healthy older adult participants aged 55 to 75 years at screening will be randomised in two cohorts; 30 obese and/or diabetic participants aged 55 to 75 years at screening will be randomised in two cohorts.

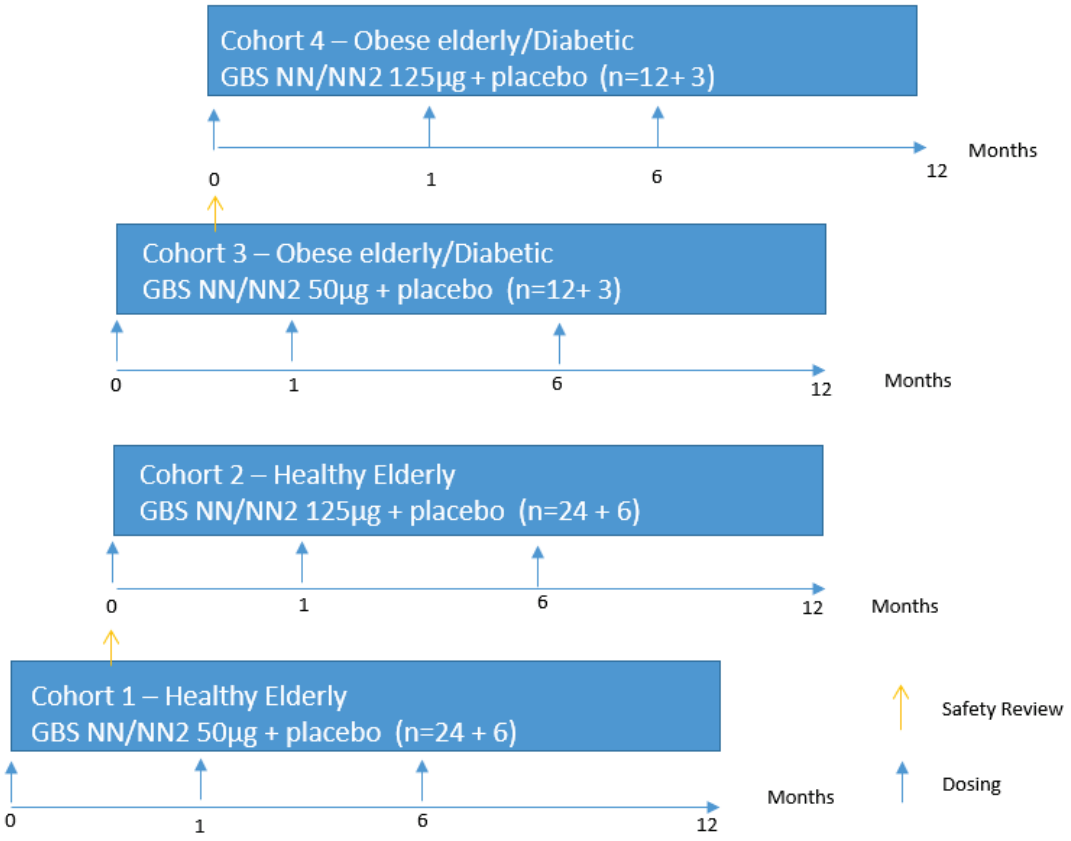
Progression from Cohort 1 to Cohort 2 and Cohort 3 will only occur after the available safety/tolerability data from all participants who completed Visit 3 in Cohort 1 have been assessed by a Safety Review Group (SRG). The SRG will review the safety data from all participants who have completed Visit 3 in Cohort 2 and Cohort 3 to determine if participants in Cohort 4 could receive the IMP.

During the study, participants will attend study visits as described in the Schedule of Activities (SoA), up to safety follow-up visit at month 12. Safety assessments will be performed and immunogenicity blood samples will be collected at study visits according to the SoA.

Safety Review Group: Yes

1.2 Schema

Figure 1 Study Schema (Refer to Section 8.10 for Study Procedures to be Considered During Special Circumstances)



GBS-NN/NN2: Group B Streptococcus vaccine containing the N-terminal domains of the Rib, Alpha C, Alpha 1 and Alpha 2/3 proteins.

1.3 Schedule of Activities

Table 1 Schedule of Activities (Refer to Section 8.10 for Study Procedures to be Considered During Special Circumstances)

	Screening Period	Treatment Period									Safety Follow-Up	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11[a]	Visit 12
Assessment	Day -28 to Day -1	Day 1	Day 8 ±1	Day 29 ±3	Visit 4 + 7±1 (Day 36)	Visit 4 + 28±3 (Day 57)	Day 99 ±7	Day 169 ±7	Visit 8 + 7±1 (Day 176)	Visit 8 + 28±3 (Day 197)	Day 237 ±14	Day 365 ±14
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demography	X											
Medical History	X											
Full physical examination	X											X
Height, Weight, BMI	X											
Vital signs[b]	X	X[c]	X	X[c]	X	X		X[c]	X	X		X
Safety laboratory tests[d]	X	X	X	X	X			X	X			
HIV[e], Hepatitis B, and C	X											

	Screening Period	Treatment Period									Safety Follow-Up	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11[a]	Visit 12
Confirmation of participant eligibility[d]		X										
Randomisation[d]		X										
IMP administration		X		X				X				
[redacted]		X	X	X	X			X	X			
Blood sample – antibody response[d]		X		X		X		X		X		X
Brief medical examination[d,f]		X		X				X				
Assessment of injection site[g]		X	X	X	X	X		X	X	X		
Completion of eDiary by participants[h]		←=========→		←=========→				←=========→				
Instruct 7-day-eDiary		X		X				X				
Review eDiary and transfer data including AE/CM			X		X				X			
Solicited AE/SAE[i]		←=========→		←=========→				←=========→				

	Screening Period	Treatment Period									Safety Follow-Up	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8	Visit 9	Visit 10	Visit 11[a]	Visit 12
Unsolicited AE/SAE[d]		←═══→			←═══→				←═══→			
AE/SAE[j]		←═══→					←═══→		←═══→	←═══→		
Concomitant medication review[k]		←═══→					←═══→		←═══→	←═══→		

AE = adverse event; BMI = body mass index; CM = concomitant medication; eDiary = electronic diary; HIV = human immunodeficiency virus; IMP = investigational medicinal product; [redacted] SAE = serious adverse event.

[a] Visit performed by telephone.

[b] Pulse rate, blood pressure, and oral temperature.

[c] Vital signs at dosing visits will be recorded pre dose and at least 30 minutes post dose.

[d] Pre dose (as applicable).

[e] Per local regulations.

[f] Symptom directed examination to confirm eligibility for discharge at least 30 minutes post dose.

[g] Thirty (30) minutes post dose on Day 1 and 30 minutes post dose on Day 29 and Day 169. Photographs may be taken of injection site reactions, as required.

[h] Participant will fill out their eDiary on a daily basis for 7 days post injection of study medication.

[i] Solicited AE/SAEs will be collected 7 days post each vaccination in the eDiary.

[j] Between Day 58 (28 days post 2nd injection) to Day 161 and from 28 days after the 3rd vaccine to Day 365 only MAAEs, AESIs, and SAEs will be collected.

[k] Between Day 1 to Day 57 and Day 162 to Day 197 all CMs will be collected. Between Day 58 to Day 161 and Day 198 to Visit 12 (Day 365): only CMs taken for MAAEs, AESIs, and SAEs, which are collected within this period will be recorded.

2.0 INTRODUCTION

2.1 Background

Streptococcus agalactiae or Lancefield's Group B Streptococcus (GBS) is a common commensal in humans, approximately 25% of all adults will be colonised with GBS at any given time.[1] Invasive GBS disease is normally associated with infection in pregnant women and new-born babies; however, invasive GBS disease in adults has been increasing over the last 40 years.[1,2] The older adult population (>65 years of age) and adults with underlying chronic health conditions (diabetes mellitus, cancer, immune suppression, obesity) are at particular risk of invasive GBS disease.[2,3]

In the United States of America (USA), it has been estimated that the majority of cases of invasive GBS occur in adults and are not related to pregnancy. Disease rates increase with age and are twice as high in the black population as in the white population. The associated mortality rate is approximately 25%.[2] The incidence of invasive GBS disease has been estimated in Belgium to be 8.2 cases/100,000 inhabitants in 2018. This has increased from 3.7 cases/100,000 inhabitants in 2009.[4]

However, non invasive GBS infections are more common than invasive infections by a factor of 3.7.[5] McLaughlin and colleagues calculated for cases where GBS was identified an overall annual hospitalisation rate of 73 (95% confidence interval [CI], 68–78) per 100,000 adults in Louisville, Kentucky USA. The hospitalisation rate varied by age; rates were 68 (95% CI, 63-74) and 100 (85–117) per 100,000 in adults 18–64 and ≥65 years of age, respectively. The highest rate of GBS-associated hospitalisation was seen among adults <65 years of age with diabetes, at 486 (95% CI, 437–540) per 100.000 annually. Overall, 20% of patients admitted to hospital were admitted to intensive care unit and an all-cause death rate of 3% was reported.[5]

Group B Streptococcus disease in non-pregnant adults causes secondary and primary bacteraemia, septic arthritis, endocarditis, prosthetic joint infection, and necrotising myositis and fasciitis.[5]

It is apparent that outside of pregnancy and the neonatal period, GBS infection results in high morbidity and mortality rates. There is no preventative treatment, cases are managed with antibiotics when an infection is diagnosed. There is a clear unmet medical need for a preventative vaccine that could provide protection to all adults but particularly to the older adult population or those at risk of infection due to underlying medical or demographic conditions. In addition, the incidence is increasing and will probably continue to increase with an increasing older adult population and an increase in the prevalence of obesity and type 2 diabetes around the world.

MinervaX has developed a novel GBS vaccine candidate designated GBS-NN/NN2, based on the N-terminal domains of the alpha protein family of GBS surface proteins. The vaccine consists of two fusion proteins each containing two N-terminal domains: GBS-NN (containing the N-terminal domains of the Rib and Alpha C proteins – RibN and AlpCN) and GBS-NN2 (containing the N-terminal domains of the Alpha 1 and Alpha 2/3 proteins – Alp1N and Alp2/3N). These alpha-like proteins (Alps) are found on most isolates of capsular polysaccharide serotypes Ia, Ib, II, III, IV, V, VI, VII, and VIII. Therefore, it is anticipated that the GBS-NN/NN2 vaccine will confer protection against close to 100% of GBS clinical isolates. Antibodies directed against the vaccine were found to recognise the vast majority of 154 clinical isolates of serotypes Ia, Ib, II, III, and V tested for antibody binding.

The MinervaX GBS-NN/NN2 vaccine is currently being evaluated for safety and immunogenicity of a primary course of two doses of 50 µg of each fusion protein (GBS-NN and GBS-NN2) in combination with 500 µg Alhydrogel®) in pregnant women, administered from 22 to 30 weeks gestational age, with a 4- and 8-week interval.

2.2 Study Rationale

In light of the increasing incidence of GBS infection in the older adult population, MinervaX wish to explore the safety and immunogenicity in this increasingly at-risk population, particularly in adults over 65 years of age.

The purpose of this planned Phase 1 trial is to study the safety and immunogenicity of two dose levels, in an older adult population, with and without underlying medical conditions (obesity and/or diabetes type 2), to assess whether the GBS-NN/NN2 vaccine could potentially be effective in an older adult population and warrant further development in this population. The trial will investigate the safety and immune response to the dose level currently under development for use in pregnant women (50 µg of each fusion protein) and a higher dose of 125 µg of each fusion protein.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

From the data gathered to date administration of GBS-NN/NN2 has been associated with mild, self-limiting pain at the injection site. No systemic risks have been identified. There have been no reports of significant or persistent reactions at the injection site.

There is a low risk of anaphylactic reactions after injection of the vaccine. All staff administering vaccines will be trained in basic or advanced life support procedure. The necessary equipment and medication for treatment would be in place when administering the vaccines, such as resuscitation equipment and medication. The participants will be observed for 30 minutes post dose.

Injection site haemorrhage may occur at the injection site in populations at increased risk of haemorrhage, such as those with thrombocytopenia or acquired/hereditary coagulation disorders. The Investigators are informed of possible injection site haemorrhage in individuals with thrombocytopenia or any coagulation disorder following study treatment administration by information included in product labels or Investigator's Brochure (IB) based on the following language in the company Core Safety Information: "As with other vaccines administered intramuscularly, all study vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an IMP administration to these participants."

There is a risk from blood sampling associated risk of discomfort, syncope, dizziness, and infection at the injection site after or during venepuncture. Blood samples will be obtained by a trained professional and medical assistance will be available.

2.3.2 Benefit Assessment

No clear benefits have been identified as efficacy has not been assessed. It is apparent that GBS-NN/NN2 induces an immune response but it is not known if the immune response is protective, as this has not been studied. The immune response generated has been shown to induce immunoglobulin G (IgG) antibodies. [redacted]

2.3.3 Overall Benefit Risk Conclusion

Considering the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with GBS-NN/NN2 with Alhydrogel® are justified by the anticipated benefits that may be afforded to older adult participants at high risk of contracting GBS infection.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GBS-NN/NN2 Recombinant Alhydrogel® may be found in the IB.

3.0 OBJECTIVES AND ENDPOINTS

Table 2 presents the primary, secondary immunological and safety objectives as well as exploratory objectives and corresponding endpoints.

Table 2 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary	
• The primary objective is to evaluate the safety and tolerability of the GBS-NN/NN2 vaccine for 4 weeks after each dose of vaccine.	• Safety and tolerability as determined by the occurrence of AEs consisting of local and systemic reactogenicity within 7 days after vaccination (Days 1 through 8 post each dose of the IMP) • Unsolicited AEs, including AESIs, MAAEs and SAEs within 28 days after each vaccination • AESIs, MAAEs, ARs/SARs leading to withdrawal from the study.
Secondary Immunological	
• To evaluate IgG antibody response to the GBS-NN/NN2 vaccine at Day 197 (principal immunological endpoint). • To evaluate IgG antibody responses induced by the three vaccine doses, on a 0-, 1- and 6-month regimen, in older adult participants 4 weeks after each vaccination. • To assess whether pre-existing antibody levels affect the vaccine-induced antibody response. • To evaluate the immune response up to 6 months following the 3rd dose; to be reported in an addendum to the main CSR.	• Geometric mean antibody concentration in µg/mL for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC). • Geometric mean fold increase in antibody concentration for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC). • Seroconversion rate (proportion of participants with a 4-fold increase above baseline – pre dose concentration) at any time post vaccination. • Proportion of participants achieving antibody concentrations for antibodies to the four individual Alps (Alp 1, Alp2/3, Rib and AlpC) above specific thresholds at Days 29, 57, 169, and 197 (these thresholds will be 1, 2, 4, and 8 µg/mL).
Secondary Safety	
• To evaluate the long-term safety profile of the GBS-NN/NN2 vaccine between Day 57 (28 days post second injection) to Day 168 and 6 months	• Proportion of participants with any SAE from between Day 57 (28 days post second injection) to Day 168 and 28 days after 3rd vaccination (Day 197) up to Day 365.

Objectives	Endpoints
following the 3rd dose (safety endpoint); to be reported in an addendum to the main CSR.	• Proportion of participants with MAAEs, AESIs, ARs/SARs requiring a medical consultation, and or leading to withdrawal from the study from 28 days after 3rd vaccination (Day 197) up to Day 365.
Exploratory	
• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted]

AEs = adverse events; AESIs = adverse events of special interest; Alps = alpha-like proteins; ARs = adverse reactions; [redacted]; CSR = clinical study report; [redacted]; GBS = Group B Streptococcus; IMP = investigational medicinal product; [redacted]; IgG = Immunoglobulin G; MAAEs = medically attended adverse events; [redacted]; SAE = serious adverse event; SAR = serious adverse reaction.

4.0 STUDY DESIGN

4.1 Overall Design

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

A schema of the trial design is shown in Section 1.2.

Eligible participants will be randomised pre dose on Day 1, once all eligibility criteria have been verified.

There will be 2 cohorts comprising 30 healthy older adult participants each and two cohorts comprising 15 obese and/or diabetic older adult participants each (see Figure 1):

- Cohort 1 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).
- Cohort 2 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS-NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).
- Cohort 3 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).
- Cohort 4 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS NN2 bound to aluminium hydroxide in a 4:1 ratio (IMP : placebo).

Eligible participants will be administered a dose of GBS-NN/NN2 or placebo on three occasions: the 1st dose will be administered on Day 1, followed by the second and 3rd doses 4 and 24 weeks later, respectively. Participants will be involved in the study for approximately one year including screening and safety follow-up. The start of the study is defined as Day 1 when participants are randomised.

Dose escalation will be managed as described in Section 4.5.

4.2 Scientific Rationale for Study Design

This study is designed as randomised, double-blind, and placebo-controlled to distinguish the effect of the IMP from other influences such as placebo effect or biased observation.

Group B Streptococcus is also associated with disease in adults particularly in the older adult and adults who are immunosuppressed. In the current study, GBS-NN/NN2 vaccine will be administered for the first time in an older adult population with and without underlying medical conditions (obesity and/or diabetes type 2) to assess whether the GBS-NN/NN2 could potentially be effective in an older adult population and warrant further development in this population.

4.3 Justification for Dose

The study will investigate the safety and immune response to the dose level currently under development for use in pregnant women (50 µg of each fusion protein) as well as a higher dose of 125 µg of each fusion protein. In the initial trial with GBS-NN alone, doses of 250 µg of the single fusion protein were administered to healthy non pregnant women. No safety concerns were reported with the maximum dose of 250 µg. Older adult participants, in whom the immune system is ageing may need a higher dose or more doses to achieve the same immune response. Hence, this study will explore the higher dose of 125 µg and a three-dose administration regimen.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last safety follow-up visit.

See Section 10.1.11 for information on early study and/or site termination.

4.5 Dose Escalation

Progression from Cohort 1 to Cohort 2 and Cohort 3 will only occur after the available safety/tolerability data from all participants who completed Visit 3 (Day 8) in Cohort 1 have been assessed by a Safety Review Group (SRG). Please see Section 9.6 for further details.

The SRG will review the safety data from all participants who have completed Visit 3 in Cohort 2 and Cohort 3 to determine if participants in Cohort 4 could receive the IMP (see Figure 1).

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Participants

Individual participants may be withdrawn for any of the reasons outlined in Section 7.0.

4.6.2 Criteria for Stopping Dose Escalation

Dose escalation will be stopped if any of the study stopping rules are met (see Section 4.6.3).

4.6.3 Criteria for Stopping the Study

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Principal Investigator (or deputy) and the Sponsor. A written document signed by the Principal Investigator (or deputy) and Sponsor will be produced ratifying the decision.

A safety review meeting will be convened to determine the progression of the study if any of the following scenarios occur:

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

If the study is temporarily halted for any reason including the circumstance where any of the above stopping criteria are fulfilled, the study will only proceed and restart once an appropriate substantial amendment has been submitted and receives regulatory approval from the Medicines and Healthcare products regulatory agency and approval from the Research Ethics Committees associated with the study.

5.0 STUDY POPULATION

Data from screening procedures will be used for treatment allocation if a procedure is not planned or repeated at Visit 2. Procedures will not be repeated at Visit 4 and Visit 8.

- The investigators should consider whether a participant with BMI ≥18 to <30 kg/m^2 and with prediabetes is eligible for Cohort 1 or 2. This decision can be made based on the CDC definition of prediabetes of an HbA1c of 5.7% to 6.4%.
- If a participant has a BMI ≥30 to ≤45 kg/m^2 and the participant has prediabetes, the participant would be eligible for Cohorts 3 and 4 as a participant who is obese.
    - For a participant to be included in Cohorts 3 and 4 as a participant with diabetes (as opposed to a participant who is obese), a pre-existing diagnosis of diabetes, documented by the general practitioner or other treating physician, is required.
    - If the participant is diagnosed with type 2 diabetes, the participant must be on treatment for type 2 diabetes; e.g. metformin, sulphonylureas or glitazones. The diabetic participant is not eligible for Cohort 3 and 4 if not receiving treatment for type 2 diabetes at study enrolment.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participants aged 55 to 75 years at screening.
2. Body mass index (BMI) ≥18 and <30 kg/m^2 for healthy participants, ≥30 to ≤45 kg/m^2 for obese participants and ≥18 to ≤45 kg/m^2 for type 2 diabetic participants at screening.
3. Able to voluntarily provide written informed consent to participate in the study.
4. Female participants must be post-menopausal.
5. Participants capable and willing to follow trial schedule and procedures.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participants who have received a GBS vaccine previously.
2. Participants with history or presence of significant (as evaluated by the investigator) cardiovascular disease, pulmonary, hepatic, gallbladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunologic, dermatological, neurological, psychiatric, autoimmune disease, or current infection.

NOTE: Patients with type 2 diabetes are to be recruited for Cohort 3 and Cohort 4. The autoimmune skin diseases, mild psoriasis and vitiligo, will not be considered as relevant for exclusion.
Other autoimmune diseases that are not stable or are progressive/worsening (as evaluated by the investigator) should lead to exclusion.

3. Laboratory values at screening which are deemed by the investigator to be clinically significantly abnormal.
4. Current or history of drug or alcohol abuse per investigator judgement.
5. Positive for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.
6. Participants currently participating in a clinical trial.
7. Participants receiving an investigational drug, vaccine or device during the 90 days preceding the initial dose in this study.
8. Any significant illness during the 4 weeks preceding the vaccination visit, per investigator judgement.
9. Participants with a history of severe allergic reactions after previous vaccination.
10. Participants who have received any vaccine within 30 days of 1st IMP administration, or who are planning to receive any vaccine (eg, travel vaccines) up to 30 days after each vaccination and/or 7 days prior to 3rd administration.
    NOTE: Exceptions could be made for emergency vaccinations (eg, tetanus) or vaccination campaigns (eg, SARS, CoV-2 or influenza) which will be permitted not less than 7 days before or after study vaccination.
11. Participants receiving immunosuppressive therapy or immunoglobulins in the 6 months prior to screening.
12. Participants within a 7-day period after an acute infection in the 7 days preceding vaccination, as per investigator judgement, or with fever (oral temperature >37.9°C) in the 72 hours preceding vaccination.
13. Participants who have received antipyretics/analgesics treatment within 72-hours prior to dosing.
14. Participants on chronic medications that are likely to affect the assessments specified in the protocol (eg, anticoagulant therapy, systemic steroids).
    NOTE: Chronic medications such as antihypertensives, bronchodilators 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. Treatment for diabetes will be continued as required for the diabetic participants recruited. Non-steroidal anti-inflammatory drugs or paracetamol will be permitted for the treatment of headache or other symptoms during the study. Use of over the counter (OTC) vitamins and dietary supplements is allowed.
15. Participants with skin defects and/or tattoos at the proposed site of vaccine administration.
16. Donation of blood or blood products within 90 days prior to 1st study vaccination.
17. Participants who, in the opinion of the Investigator, are unsuitable for participation in the study.

18. Involvement in the planning and/or conduct of the study (applies to both Sponsor personnel and/or personnel at the study centre or Clinical Research Organisation [CRO]).

5.3 Lifestyle Considerations

No restrictions pertaining to lifestyle and/or diet beyond the details indicated in Section 5.2.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

If the investigator believes there is a reasonable justification to do so, screening procedures may be repeated (maximum one rescreening per participant is allowed).

Only laboratory results from the rescreening visit, if it occurs, will be taken into consideration and recorded in the electronic case report form (eCRF). Medical history (MH), physical examination and review of inclusion/exclusion criteria must be repeated if a rescreening visit occurs. The participant can only be randomised once the investigator receives the results and confirms the eligibility criteria.

5.5 Criteria for Temporarily Delaying

Vaccination may be postponed within the allowed time interval until any transient circumstances have been resolved.

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

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

- Acute infection in the 7 days before the vaccination, per investigator judgement.
- Fever (oral temperature >37.9°C) in the 72 hours preceding vaccination.

6.0 INVESTIGATIONAL MEDICINAL PRODUCT(S) AND CONCOMITANT THERAPY

6.1 Investigational Medicinal Product(s) Administered

The GBS-NN/NN2 vaccine will be supplied as two sterile solutions (GBS-NN and GBS-NN2) to be mixed with a sterile dilution buffer and adsorbed to Alhydrogel® adjuvant. The placebo vaccine will be 0.9% saline for injection.

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 (eg, due to an ongoing injection site reaction, or tattoo), or the participant prefers to receive the vaccine in the dominant arm.

The procedure for the assembly of both dose levels for the study is described in detail in the IMP handling Manual.

Individual participant treatments will be reconstituted and dispensed by the investigator or designee.

The following dosing strategy will be employed:

Cohort	Population	Dose scheduled	Dose level GBS-NN/NN2 or placebo
1	Healthy older adult participants	Visit 2 Visit 4 Visit 8	50 µg of each protein or placebo
2	Healthy older adult participants	Visit 2 Visit 4 Visit 8	125 µg of each protein or placebo
3	Obese and/or diabetic older adult participants	Visit 2 Visit 4 Visit 8	50 µg of each protein or placebo
4	Obese and/or diabetic older adult participants	Visit 2 Visit 4 Visit 8	125 µg of each protein or placebo

6.2 Preparation, Handling, Storage, and Accountability

Refer to IMP Handling Manual for details regarding preparation, handling, storage, and accountability of IMP.

Only participants enrolled in the study may receive IMP, and only authorised unblinded study site staff may supply and/or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the unblinded authorised study site staff.

The unblinded study team (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The unblinded study staff must maintain an adequate record of the receipt and distribution of all IMPs using the Drug Accountability Form. These forms must be available for inspection at any time.

At the end of the study, following IMP reconciliation, unused medication will be returned to the Sponsor or destroyed locally, if destroyed locally a destruction certificate is required.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Participant Identification

Participant identification numbers will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to the study site. Re-screening of participants will require the allocation of a new participant identification number.

6.3.2 Treatment Allocation to the Participant

Allocation of the participant to treatment within a cohort at the study site will be performed using a randomisation module of the electronic case report form (eCRF) used as Interactive Response System (IRS) at the site after confirming eligibility and prior to 1st dosing. The following series of randomisation numbers will be used for the four cohorts: 1001 to 1030, 2001 to 2030, 3001 to 3015, and 4001 to 4015.

6.3.3 Blinding

Data will be collected in a double-blind manner. The study participant and those responsible for the evaluation of any study endpoint (eg, safety and immunogenicity) will all be unaware of which IMP was administered. To do so, IMP preparation and administration will be done by authorised personnel who will not participate in any of the study clinical evaluations.

The laboratory conducting the laboratory testing will be blinded to the treatment, and codes will be used to link the participant and study (without any link to the treatment attributed to the participant).

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

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

The randomisation list will be generated by a validated statistical analysis system (SAS) programme and kept in a restricted access folder and will subsequently be integrated in the eCRF.

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

6.3.3.1 Emergency Unblinding

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

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

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

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

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

The information in this section will, if applicable, be described in more detail in a study specific blinding manual.

Participants may continue their participation in the study even if their treatment assignment is unblinded.

6.4 Investigational Medicinal Product Compliance

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

6.5 Dose Modification

Dose modifications are not planned or allowed in this study.

6.6 Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications (CM) will be recorded in the electronic diary (eDiary) of the participant 7 days after each vaccination. Study staff will review the eDiary and transfer relevant AEs and CM data into the eCRF.

NOTE: The overall collection of CMs during the study period should be done as follows (see Section 8.3.1 for AE collection details):

- *Day 1 – Visit 6 (Day 57): All CMs associated with an AE.*
- *Day 58 – Day 161: Only CMs taken for MAAEs, AESIs, and SAEs, which are collected within this period.*
- *Day 162 (7 days prior to 3rd vaccination at Visit 8) – Visit 10 (Day 197): All CMs associated with an AE.*
- *Day 198 – Visit 12 (Day 365): Only CMs taken for MAAEs, AESIs, and SAEs collected within this period.*

6.6.1 Permitted Concomitant Medications

Participants may take concomitant chronic medications such as antihypertensives, bronchodilators or statins that do not affect the immune system during the study at the discretion of the investigator. Treatment for diabetes will be continued as required for the diabetic participants recruited. Non-steroidal anti-inflammatory drugs or paracetamol at doses of ≤4 g/day, will be permitted for use any time during the study, except within 72 hours before each vaccination, for the treatment of headache or other symptoms.

6.6.2 Prohibited Concomitant Medications

The following medications are prohibited, as defined by the exclusion criteria (Section 5.2):

- Immunosuppressive therapy or immunoglobulins in the 6 months prior to screening.
- Chronic medications that are likely to affect the assessments specified in the protocol (eg, anticoagulant therapy, systemic steroids).
- Vaccines within 30 days of 1st IMP administration and up to 30 days after each study vaccination and 7 days prior to 3rd IMP administration, with the exception of emergency vaccinations or vaccination campaigns, which will be permitted not less than 7 days before and after study vaccination.

7.0 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Investigational Medicinal Product

If IMP is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the Schedule of Activities (SoA) in Section 1.3 for data to be collected at the time of discontinuation of IMP and follow-up and for any further evaluations that need to be completed. The primary reason for the investigator's decision, must be specified in the end of study form in the eCRF.

If a participant who does not meet enrolment criteria is inadvertently enrolled, that participant should be discontinued from IMP and the Sponsor, or Sponsor designee, must be contacted. An exception may be granted in rare circumstances, and in these rare cases, the investigator must obtain documented approval from the Sponsor, or Sponsor designee, to allow the participant to continue in the study.

Participants who discontinue prior to 1st IMP administration will be replaced. Vaccinated participants will not be replaced unless enrolled in error.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of investigational product for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Hy's Law or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant (see Section 10.4).

7.2 Participant Discontinuation/Withdrawal from the Study

Dosing for any individual participant will be stopped if the participant experiences a serious adverse event (SAE) or a clinically significant possibly drug-related related AE, which in the opinion of the study physician, Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the study for that participant's wellbeing.

A participant is free to leave the study at any time without giving reason for this according to the Declaration of Helsinki.

Should a participant want to withdraw from the study after he/she has been vaccinated, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Participants withdrawing due to an AE should be followed up according to the follow-up visit schedule (see SoA [Section 1.3]).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she fails to return for a scheduled visit and is unable to be contacted by the study site after at least three attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's clinical report form.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue investigational product.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Safety/laboratory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The order of each procedure will be determined by the study site. However, when multiple procedures are scheduled at the same day, they all need to be performed before the administration of the IMP takes place.

During special circumstances (eg, a pandemic), the specific guidance from local public health and other competent authorities regarding the protection of participants' welfare must be applied. In such special circumstances, certain study procedures may be implemented for enrolled participants (refer to Section 8.10 for further details).

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

The description of safety assessments is given below, and the timings of these assessments is given in the SoA (Section 1.3). Unscheduled assessments may be performed at the discretion of the Investigator.

8.2.1 Physical Examinations

Full physical examinations will be performed at screening and safety follow-up.

A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height, weight and BMI will also be measured and recorded at screening.

Physical examination abnormalities noted at the screening visit should be recorded in the participant's MH.

A brief physical examination will be performed at dosing visits prior to study vaccination, and it will include a symptom directed examination to confirm eligibility for discharge at least 30 minutes post dose.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs measurements will be performed at time points indicated in the SoA (see Section 1.3).

Vital signs will be measured in a sitting position after 5 minutes rest and will include oral temperature, systolic and diastolic blood pressure, and pulse rate.

Vital signs at dosing visits will be recorded pre dose and at least 30 minutes post dose.

8.2.3 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

Table 3 presents number of tests, volumes of blood per test and total volume of blood.

Table 3 Number of tests, volumes of blood per test and total volume of blood

	Number of tests	Volume of blood per test, mL	Total blood volume, mL
Biochemistry	7	10	70
Haematology	7	5	35
HIV, Hepatitis B, and C	1	10	10
Immunogenicity	6	15	90
[redacted]	[redacted]	[redacted]	[redacted]
Total blood volume, mL			445

HIV = human immunodeficiency virus; [redacted]

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded as an unscheduled visit.

8.2.4 Electronic Diary

The participant will get access to an eDiary at Visit 2, when vaccine/placebo is administered. In the eDiary, the participant is asked to record details of solicited local and systemic reactions for 7 days after each of the vaccinations (the day of the vaccination and the following 6 days).

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

For solicited systemic reactions (chills, muscle pains/myalgia, malaise, nausea, vomiting, headache, and fatigue), intensities (mild, moderate, or severe) should be recorded in the eDiary by the participant. In addition, other AEs, ie, unsolicited AEs, including medically attended AEs (MAAEs), SAEs, CM and/or vaccines should also be recorded and assessed in the eDiary.

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

If serious, the SAEs will undergo evaluation as per the current reference safety information of the IB, as described in Section 6.0.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the 1st IMP administration until the follow-up visit at the time points specified in the SoA (Section 1.3).

NOTE: The overall collection of AEs during the study period should be done as follows:

- *Day 1 – Visit 6 (Day 57): All AEs*
- *Day 58 – Day 161: Only MAAEs, AESIs, and SAEs*
- *Day 162 – Visit 10 (Day 197): All AEs*
- *Day 198 – Visit 12 (Day 365): Only MAAEs, AESIs, and SAEs*

Medical occurrences that begin before the start of IMP administration but after obtaining informed consent will be recorded as MH, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the investigator's awareness of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the investigational product or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.3.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All adverse reactions (ARs) and SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of an IMP under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, EU Eudravigilance Database (as applicable), IRBs/IECs, and Investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment will be collected by the participant in a solicited AE eDiary for 7 days following each study vaccination. The set of solicited AEs associated with reactogenicity are presented in Table 4.

Table 4 Reactogenicity Assessment: List of solicited adverse events

Local	Systemic
Pain at the site of injection	Fever (>100°F [>37.9°C])[a]
Erythema/redness at the site of injection	Chills
Tenderness	Muscle pains
Induration/swelling at the site of injection	Fatigue
Itching	Headache
	Malaise
	Nausea
	Vomiting

[a] Fever measured orally. Investigators who consider a temperature lower than this cutoff as a fever or a 'fever' reported by participants without documentation by a thermometer should record the event as 'elevated body temperature'.

8.3.6 Adverse Events of Special Interest and Medically Attended Adverse Events

Adverse events will be monitored throughout the study to identify any event of interest that may indicate a trend or risk to participants. The following are considered adverse events of special interest (AESI):

- Development of autoimmune diseases
- GBS infections
- Symptomatic GBS urinary tract infections

A MAAE is an AE that leads to an unscheduled visit to a health care provider.

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Immunogenicity and Peripheral Blood Mononuclear Cell Assessments

Instructions for the collection, labelling and handling of biological samples will be provided by the Sponsor in the sample handling manual.

8.7.1 Immunogenicity Assessments

Serum samples for immunogenicity assessments will be collected according to the SoA (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the sample handling manual. Results for exploratory immunogenicity analyses may be reported separately from the clinical study report (CSR).

8.7.2 [redacted]

[redacted]

8.8 Biomarkers

Serum samples will be assayed in a validated enzyme-linked immunosorbent assay (ELISA) to measure the concentrations of IgG specific for the four Alps (Alp 1, Alp 2/3, AlpC, and Rib). Potentially anomalous results will be discussed with the Sponsor, without revealing the identity of the participants.

8.9 Health Economics

Health economics parameters are not evaluated in this study.

8.10 Study Procedures During Special Circumstances

During special circumstances (eg, a pandemic), the specific guidance from local public health and other competent authorities regarding the protection of participants' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a telephone call, other means of virtual contact, or home visit, if appropriate.
- Biological samples may be collected at the participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If, despite best efforts, it is not possible to collect blood samples within the interval predefined in the protocol, then the interval for blood sampling may be extended up to a maximum length of 30 days before the next blood sampling. Impact on the per-protocol set for analysis of immunogenicity will be determined on a case-by-case basis.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses are to be tested.

9.2 Sample Size Determination

A total of 90 participants are planned. There will be two cohorts comprising 30 healthy older adult participants each and two cohorts comprising 15 obese and/or diabetic older adult participants each. Cohort 1 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS-NN2 bound to aluminium hydroxide (24 healthy older adult participants) or placebo (6 healthy older adult participants). Cohort 2 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS-NN2 bound to aluminium hydroxide (24 participants) or placebo (6 healthy older adult participants). Cohort 3 will receive three injections, each consisting of 50 µg of GBS-NN and 50 µg of GBS NN2 bound to aluminium hydroxide (12 obese and/or diabetic older adult participants) or placebo (3 obese and/or diabetic older adult participants). Cohort 4 will receive three injections, each consisting of 125 µg of GBS-NN and 125 µg of GBS-NN2 bound to aluminium hydroxide (12 obese and/or diabetic older adult participants) or placebo (3 obese and/or diabetic older adult participants).

Sample size has been selected to provide a preliminary assessment of vaccine safety and tolerability by cohort, as well as to provide a preliminary assessment of immunogenicity.

The sample size is not based on statistical considerations but is typical for studies of this nature and is considered adequate to characterise the distribution of the planned endpoints. Any statistical testing will be considered exploratory and descriptive.

9.3 Analysis Sets

The analysis sets are defined in Table 5.

Table 5 Analysis Sets

Analysis Set	Description
Entered Analysis Set	All participants who sign the ICF.
Enrolled Analysis Set	All participants who have met all eligibility criteria.
Safety Analysis Set	All participants randomly assigned to study treatment and who take at least one dose of the IMP. Participants will be analysed according to the treatment they actually received.
Immunogenicity Analysis Set	All participants in the Safety Analysis Set with at least one post dose blood sample collected and analysed for immunogenicity. Participants will be summarised according to treatment received.
Per-protocol Set	All participants who receive all three doses of the study vaccine and provide evaluable samples for analysis of the principal immunological endpoint without any protocol deviation that could lead to its exclusion.

The primary and secondary safety analyses will be performed on the safety analysis set. The secondary immunological analyses will be performed on the immunogenicity analysis set. The "principal" immunological analysis will also be performed on the per-protocol set if the number of participants in the per-protocol set differs by more than 5% from the number of participants in the safety analysis set.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the participant analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries, and listings will be performed using the SAS® software (version 9.4 or higher).

The following descriptive statistics will be used as applicable to summarise the study data unless otherwise specified:

- Continuous variables: sample size [n], mean, standard deviation [SD], median, minimum [min], and maximum [max].
- Categorical variables: frequencies and percentages.

Individual participant data will be presented in listings.

9.4.1 Safety Analysis

The percentage of participants with at least one solicited AE (local and systemic), with at least one unsolicited AE, and with any AE during the 7-day or the 28-day follow-up period will be tabulated after each vaccination and overall. Similar tabulation will be done for Grade 3 events, any AESIs, any MAAEs, any AEs considered related to the vaccination and any Grade 3 AEs considered related to vaccination.

The percentage of participants reporting each individual solicited local and general AE during the 7-day follow-up period will be tabulated over the three doses.

The percentage of participants with unsolicited AEs, including AESIs, MAAEs and SAEs within 28 days after any doses will be tabulated by treatment and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs and for Grade 3 and causally related unsolicited AEs and for unsolicited AEs causally related to vaccination.

The number of participants who experienced at least one SAE during the entire study period will be reported. The number and percentage of participants with AESIs, MAAEs, AEs/SAEs, and ARs/SARs leading to withdrawal from the study or discontinuation of the treatment will be tabulated.

The number and percentage of participants with any SAE, AESIs, MAAEs, ARs/SARs leading to withdrawal from the study between Day 57 (28 days post second injection) to Day 168 and from 28 days after 3rd vaccination up to Day 365 will also be summarised by treatment group.

All laboratory test results, and vital signs measurements will be summarised for each treatment group using descriptive statistics at each visit for observed and change from baseline values. The incidence of treatment-emergent abnormal laboratory values will also be summarised using descriptive statistics.

Further details will be provided in the SAP.

9.4.2 Analysis of Immunogenicity

Geometric mean concentrations and their 95% CIs will be presented for each treatment and at each timepoint that blood samples are collected for antibody response specific for the four Alps (Alp1, Alp2/3, AlpC and Rib). Fold-change from baseline values specific for the four Alps (Alp1, Alp2/3, AlpC and Rib) will be summarised similarly (data permitting).

Proportion of participants with a four-fold increase (seroconversion) above baseline (pre dose concentration) at each time point post vaccination will be summarised. Number and proportion of participants achieving antibody concentrations above a specific threshold (1, 2, 4, and 8 µg/mL) at each timepoint will also be tabulated similarly.

Exploratory comparisons between the four Alps (Alp1, Alp2/3, AlpC and Rib) and placebo within healthy older adult and obese/type 2 diabetic older adult participants may be performed using linear mixed models. Model may include age, gender, or other covariates, as relevant. More details will be provided in the SAP.

9.4.3 Missing Data

Missing data will not be imputed.

9.5 Interim Analysis

No interim analysis is planned.

9.6 Safety Review Group

An SRG is responsible for ongoing safety monitoring for the clinical conduct of the study and meets on a regular basis.

The SRG will be responsible to assess safety after all participants have completed Visit 3 (Day 8) for Cohort 1, at which point the decision will be made as to whether proceeding with administration of the doses in Cohorts 2 and 3 is appropriate. Safety in Cohorts 2 and 3 will be assessed by the SRG after all participants have completed Visit 3 at which point the decision will be made by the SRG as to whether proceeding to Cohort 4 is appropriate.

Details of the compositions and responsibilities of the SRG will be provided in the SRG charter.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences international ethical guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at site if the investigator has not signed the protocol.

10.1.2 Adequate Resources

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

10.1.5 Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.

The clinical report form must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF during their participation in the study.

A copy of the ICF must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor or designee. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law and the General Data Protection Regulation (GDPR, Ref. 3). The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her clinical report forms may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Committees Structure

This study does not have an independent safety monitoring committee.

10.1.8 Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- Guidance on eCRF will be provided to the investigator in a separate document.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.
- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Study Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organisations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10 Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous clinical report forms or transfer records, depending on the study. Also, current clinical report forms must be available.

Definition of what constitutes source data and its origin can be found in source data identification log.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further IMP development.

For study site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Refer to Section 4.4 for the End of Study definition.

10.1.12 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the investigator and study site will be set forth in the Clinical Trial Agreement.

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the local laboratory. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.0 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Haematology	Platelet count	White blood cell count with differential white blood cell (Absolute and percentages):
	Red blood cell count	Neutrophils
	Haemoglobin	Lymphocytes
	Haematocrit	Monocytes
	Red blood cell indices:	Eosinophils
	Mean corpuscular volume	Basophils
	Mean corpuscular haemoglobin	
	Mean cell haemoglobin concentration	
	%Reticulocytes	
Clinical Chemistry[a]	Creatinine	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase
	Gamma glutamyl transferase	
	Urea	
	Potassium	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase
	Sodium	
	Lactate dehydrogenase	Creatine kinase
	Albumin	Creatine kinase myocardial band (CK-MB) fraction will be performed if clinically indicated
	C-reactive protein	
	Total protein	
	Globulin (Calculated by: total protein – albumin)	
	Total and direct bilirubin	
Viral serology	Human immunodeficiency virus (HIV)	Hepatitis C virus
	Hepatitis B surface antigen	
Glycosylated haemoglobin	Haemoglobin A1C	

Laboratory Assessments	Parameters

NOTES:

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.4. All events of ALT or AST ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Investigational Medicinal Product

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with that product. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of IMP, whether or not considered related to the IMP.

Timing for the collection of AEs, definition of Unsolicited and Solicited AE
• All AEs, AESIs, and SAEs will be collected from the 1st IMP administration. • Solicited AEs are predefined events/symptoms that the participant is specifically asked to record in the eDiary. The predefined solicited AEs include: Injection site reactions (redness, swelling, pain, tenderness, and itching) and systemic reactions (pyrexia, chills, muscle pains/myalgia, malaise, nausea, vomiting, headache, and fatigue). • An AE reported in response to an open question e.g., "Did you experience any other signs/symptoms?", is an unsolicited AE. • An unsolicited AE is an AE reported spontaneously by the participant. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the study site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified study site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition detected or diagnosed after IMP administration even though it may have been present before the start of the study.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (eg, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE and SUSAR

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

- For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Other situations:

- Medical or scientific judgement should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

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

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event if available or if applicable and determine if the event meets any criterion for an SAE.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- 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.

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.
- The following definitions will be used:
    - A reasonable possibility of being related
    - No reasonable possibility of being related
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to IMP will be considered "related." Events assessed as having no reasonable possibility of being related to IMP will be considered "unrelated."
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information, the CRF will be amended accordingly, if the AE is also a SAE an updated SAE form will be sent to the pharmacovigilance provider.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This

may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide the Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the investigator's awareness of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the paper SAE report form. The study site will submit the SAE report form, via email, within 24 hours of the investigator's awareness of the event. Facsimile transmission may be utilised as an alternative mode of submission, if necessary.
- Notification of SAE information via telephone does not replace the need for the investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the investigator's awareness of the event.
- Contacts for SAE reporting are as follows:

  ProPharma Group
  Olliver
  Aske
  Richmond
  North Yorkshire
  DL10 5HX
  Tel: 00 44 (0) 1279 406759
  Fax: 00 44 (0) 1279 418964
  Email: pvservices@propharmagroup.com

10.3.5 Reporting of SUSARs

SUSARs Reporting

- The Sponsor or designee shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) is reported as soon as possible to the competent authorities and ethics committees.
- Reporting of SUSARs needs to follow all local and international leal requirements.
- Reporting needs to be done not later than seven days after the Sponsor was first aware of the reaction. Any additional relevant information should be sent within eight days of the report.

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

The contact details of the pharmacovigilance provider are as follows:

ProPharma Group
Olliver
Aske
Richmond
North Yorkshire
DL10 5HX
Tel: 00 44 (0) 1279 406759
Fax: 00 44 (0) 1279 418964
Email: pvservices@propharmagroup.com

10.4 Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or alanine aminotransferase (ALT) ≥3 × ULN together with total bilirubin (TBL) ≥2 × ULN and confirmed as a Hy's Law case should be reported as an SAE.

Hy's Law

AST or ALT ≥3 × ULN together with TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

10.5 Appendix 5: Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
Alps	Alpha-like proteins
ALT	Alanine aminotransferase
AR	Adverse Reaction
AST	Aspartate aminotransferase
BMI	Body mass index
CA	Competent authority
CFR	Code of Federal Regulations
CI	Confidence interval
CM	Concomitant medication(s)
COVID-19	Coronavirus disease 2019
CRO	Clinical research organisation
CSR	Clinical study report
eCRF	Electronic case report form
eDiary	Electronic diary
GBS	Group B Streptococcus
GCP	Good clinical practices
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalised ratio
IRT	Interactive response technology
MAAE	Medically attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical history

Abbreviation	Definition
OTC	Over the counter
[redacted]	[redacted]
PI	Principal investigator
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical analysis system
SD	Standard deviation
SoA	Schedule of activities
SRG	Safety review group
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
ULN	Upper limit of normal
USA	United States of America

11.0 REFERENCES

1. Edwards MS, Baker CJ. Group B streptococcal infections in elderly adults. *Clin Infect Dis*. 2005;41(6):839-847.
2. Farley MM. Group B streptococcal disease in nonpregnant adults. *Clin Infect Dis*. 2001;33(4):556-561.
3. Sendi P, Johansson L, Norrby-Teglund A. Invasive group B Streptococcal disease in non-pregnant adults: a review with emphasis on skin and soft-tissue infections. *Infection*. 2008;36(2):100-111.
4. Graux E, Hites M, Martiny D, et al. Invasive group B Streptococcus among non-pregnant adults in Brussels-Capital Region, 2005-2019. *Eur J Clin Microbiol Infect Dis*. 2021;40(3):515-523.
5. McLaughlin JM, Peyrani P, Furmanek S, et al. Burden of Adults Hospitalized With Group B Streptococcal Infection. *J Infect Dis*. 2021;224(7):1170-1178.

Signature of Investigator

PROTOCOL TITLE: A randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability and immunogenicity of three doses of Group B Streptococcus vaccine (GBS-NN/NN2 with Alhydrogel®) in elderly participants aged 55 to 75.

PROTOCOL NO: MVX0006

VERSION: 2.0, 19 January 2023

This protocol is a confidential communication of MinervaX. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study centre in which the study will be conducted. Return the signed copy to Sponsor or CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

_____

_____